REMARKS

Claim Amendments

Claims 15 and 16 have been amended to direct the treatment to specifically colorectal cancer, thereby requiring the cancellation of claims 21 and 24.

Claims 15 and 16 have also been amended to remove the *specific recitation* of administering an effective amount of "5 FU and CPT 11" in combination with an effective amount of AZD2171, as being an unnecessary limitation.

These amendments are being made without disclaimer or prejudice to Applicant's right to pursue any subject matter thereby deleted in one or more continuing applications. Following entry of the above amendments, claims 15-17 are pending in this application.

Double Patenting

The prior obviousness-type double patenting rejection has been withdrawn and replaced with a new obviousness-type double patenting rejection. Specifically, at page 3 of the Action, the Examiner states that claims 15-17, 21, and 24 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 3, 4, and 15 of copending Application No. 10/563,439, or alternatively over claims 12-18 of 10/594,234; claims 21-24, 27, 28, and 31-34 of 10/594,235; claims 11, 12, and 15-24 of 11/994,824; claims 11-17 of 12/158,266; or claims 13-21 of 12/408,833 in view of Hennequin et al (WO 00/47212). The Examiner's attention is called to the current status of these cited applications:

- Application 10/563,439 has been abandoned in favor of continuation application 12/555,592, which is currently undergoing pre-exam processing.
- Application 10/594,234 is currently pending with no allowed claims, with a final rejection having been mailed on March 31, 2010.
- Application 10/594,235 is currently pending, with a final rejection having been mailed December 22, 2009.
- Application 11/994,824 is currently pending with a non-final rejection having been mailed March 23, 2010.
- Application 12/158,266 is currently pending with a final rejection having been mailed on March 12, 2010.

- Application 12/408,833 is currently pending with a non-final Action having been mailed April 15, 2010.

This obviousness-type patenting rejection thus remains *provisional*. While Applicant does not agree with the Examiner's argument of obviousness-type double patenting, Applicant need not, and in fact cannot respond to this ground for rejection unless and until claims are allowed in one or more of the reference applications before allowance of the present application.

Claim Rejections - 35 USC § 103

At page 5 of the Action the Examiner notes that Applicant's arguments have overcome the previous rejection of claims 15-18, 20-21, and 24 under 35 USC 103(a), and that therefore, this prior rejection has been withdrawn. However, the Examiner has made a new obviousness rejection. Specifically, claims 15-17, 21, and 24 are newly rejected under 35 U.S.C. 103(a) as being unpatentable over Hennequin et al, WO 00/47212 (hereinafter "Hennequin").

In support of this new rejection the Examiner asserts that Hennequin teach administration of quinazoline derivatives as angiogenesis inhibitors, such as solid tumors (citing the abstract and pages 83 and 86), and exemplify AZD2171 (Example 240); that Hennequin further teach that, "in the field of medical oncology, it is normal practice to use a combination of different forms of treatment to treat each patient with cancer, including radiotherapy and chemotherapy; antiproliferative/antineoplastic drugs and combinations thereof which may be used include 5-fluorouracil (5-FU) and irinotecan (CPT-11)," citing pages 85 and 86 of the reference.

The Examiner acknowledges that Hennequin do not specifically teach the combination of AZD2171 with 5- fluorouracil and/or irinotecan, but asserts that it would have been obvious to a person having ordinary skill in the art at the time the invention was made to administer 5-fluorouracil and/or irinotecan with AZD2171, thus arriving at the claimed invention. In support of this assertion the Examiner argues that one skilled in the art would be motivated to do so because Hennequin "fairly teach and suggest the administration of antiproliferative/antineoplastic drugs and combinations thereof including 5-fluorouracil (5-FU) and irinotecan (CPT-11), such that it would be within the purview of the skilled artisan to select said compounds for administration by routine experimentation, in order to optimize the efficacy of the resultant composition."

This new ground for rejection is respectfully traversed.

The Hennequin Disclosure Generically Encompassing Combinations with Essentially Any Type of Cancer Therapy Does Not Give Rise to *Prima Facie* Obviousness of the Presently Claimed Combination Therapy

Hennequin discloses the use of compounds of formula I, as well as a number of specific compounds including ZD2171 (see page 3, line 1 to page 9, line 23 and Example 240 of Hennequin), in the production of an antiangiogenic and/or vascular permeability reducing effect, as well as the use of compounds of formula I in the treatment of a cancer, including tumours of the colon (see pages 1-2 and 86, lines 11-23). Hennequin also provides some general teaching on the possibility of administering the compounds of formula I in combination with one or more other substances and/or treatments such as surgery, radiotherapy or chemotherapy (see page 84, line 30 to page 86, line 10 of Hennequin). The chemotherapy is further noted as covering three main broad generic categories of therapeutic agents, being "other antiangiogenic agents," "cytostatic agents" and "antiproliferative/antineoplastic drugs," citing other generic sub-categories and certain examples under each, including (among many others) under antiproliferative/antineoplastic drugs, antifolates such as 5-fluorouracil and topoisomerase inhibitors such as irinotecan (see page 85, line 27 and page 86, line 2).

As the Examiner acknowledges, however, there is no disclosure in Hennequin of a specific combination of ZD2171 with either 5-FU or CPT-11. The disclosure of Hennequin to which the Examiner refers is simply a *generic* omnibus statement that an antiangiogenic and/or vascular permeability reducing treatment using one of the vast number of generically disclosed or specifically named angiogenesis inhibitors may be combined with one or more other substances or treatments, and then proceeds to list a vast number possible treatments and generically disclosed or specifically named chemotherapeutic agents. No preference is expressed for any particular angiogenesis inhibitor to use in such a combination, and the *only* preference with respect to the *other* agent of such a combination is at 86, lines 7-10, noting a combination of the vascular targeting agent N-acetylcolchinol-O-phosphate (which clearly is nether an antifolate nor a topoisomerase inhibitor) with "a compound of formula I as defined hereinbefore." It is respectfully submitted that there is nothing in the disclosure of Hennequin, *when considered as a whole*, that would suggest or otherwise lead the skilled person to specifically select 5-FU or

CPT-11 out of the enormous listing of generic and "for example" possibilities and then specifically select, out of the broad generic teachings and hundreds of examples of Hennequin compounds, to combine it with the compound of Example 240, AZD2171, and then administer the combination specifically for the treatment of colorectal cancer as presently claimed.

When considering a prior art reference, it is required to consider the reference *as a whole* and not just select out isolated disclosures for combination, which the Examiner could *only* have done by impermissible use of hindsight. It is therefore respectfully submitted that Hennequin does not give rise to *prima facie* obviousness. Accordingly, it is respectfully requested that this obviousness rejection be withdrawn.

Any *Prima Facie* Obviousness That Might be Asserted is Overcome by the Comparative Tests and Figures in the Present Specification Showing Significantly Greater Efficacy of the Claimed Combination Compared to Either Component Alone

Even if a case of *prima facie* obviousness had been made, any such *prima facie* obviousness is overcome by the comparative data presented in the specification at pages 34-39 and in Figures 1-4. The Examiner states at page 6 of the Action that "Applicant's data in the specification has been fully considered, but is not deemed persuasive for overcoming the rejection." However, it is respectfully requested that the Examiner reconsider this comparative data in view of the above claim amendments, and under what is respectfully submitted to be the more appropriate criteria for evaluating the comparative data discussed below.

The tests and resulting data presented in the specification at pages 34 through 39 and in Figures 1-4 demonstrate the activity of AZD2171 when dosed in combination with 5-FU or CPT-11 relative to each component dosed separately, in the treatment of human LS-174T colon tumour xenografts in *nude* mice.

In **test (a)** AZD2171 and 5-FU were dosed separately and in combination with AZD2171 dosed at 3 mg/kg or 1.5 mg/kg, and the results are shown in Figures 1 and 2, respectively. As stated at the bottom of page 36, the combination of 5-FU with AZD2171 dosed at 3 mg/kg produced "a significantly greater inhibition of tumour growth" than 5-FU alone or AZD2171 alone (Figure 1); and the inhibition of tumour growth produced by the combination of the two agents AZD2171 and 5-FU was still greater than that produced by either agent alone when the dose of AZD2171 was reduced to 1.5 mg/kg (Figure 2).

In **test (b)** AZD2171 and CPT-11 were dosed separately and in combination with AZD2171 dosed at 3 mg/kg or 1.5 mg/kg, and the results are shown in Figures 3 and 4, respectively. As reported in the second full paragraph on page 39, the combination of CPT-11 with AZD2171 dosed at 3 mg/kg or 1.5 mg/kg produced "a significantly greater inhibition of tumour growth" than CPT-11 alone or AZD2171 alone (Figures 3 and 4).

However, the Examiner has essentially disqualified each test at both dose levels of AZD2171, asserting that the tests are inconsistent with the specification and/or not commensurate in scope with the claims.

With respect to test (a), the Examiner disregards the 3 mg/kg AZD2171 data on the assertion that:

> ... of the dosages administered in the data for AZD2171 (1.5 mg/kg and 3 mg/kg), only one dosage is considered to be "therapeutically effective", since the specification elsewhere teaches that therapeutically effective dosages of AZD2171 are in the range of 0.01-1.5 mg/kg (see page 31, lines 20-25 of the specification).

(Action at page 7).

The Examiner then disregards the 1.5 mg/kg AZD2171 comparative data on the assertion that:

> Regarding the data for the administration of 1.5 mg/kg AZD2171 with 50 mg/kg 5-FU (Figure 2), these results do not appear to show "significantly better" results over the use of AZD2171 alone; the results up to day 25 appear to overlap statistically, and at day 25, there appears to be no improved effect from the combination of AZD2171 and 5-FU over the use of AZD2171 alone.

(Action at page 7).

With respect to test (b), it is understood that the Examiner has also disregarded the 3 mg/kg AZD2171 data on the same assertion noted above, that:

> ... of the dosages administered in the data for AZD2171 (1.5 mg/kg and 3 mg/kg), only one dosage is considered to be "therapeutically effective", since the specification elsewhere teaches that therapeutically effective dosages of AZD2171 are in the range of 0.01-1.5 mg/kg (see page 31, lines 20-25 of the specification).

(Action at page 7).

The Examiner then disregards the 1.5 mg/kg AZD2171 comparative data with 25 mg/kg CPT-11 (Figured 4), even though demonstrating "significantly better" results, on the assertions that "the results are not commensurate in scope with the claims as currently written":

> First, only 1.5 mg/kg of AZD2171 is tested, but the specification teaches that an "effective dose" (as currently claimed) is 0.01-1.5 mg/kg (page 31); therefore, the full range of effective amount has not been tested, and it is not clear that one skilled in the art could ascertain a trend from the single dosage tested to extend the probative value thereof.

and:

> Second, only one dosage of CPT-11 is tested (25 mg/kg), but the specification teaches that CPT-11 may be administered "in accordance with any known route of administration and dosage", for example 350 mg/m2 as an intravenous infusion (page 31); therefore, it is not clear if the full range of effective amounts have been tested, and it is not clear that one skilled in the art could ascertain a trend from the single dosage tested to extend the probative value thereof.

(Action at pages 7-8).

It is respectfully submitted that in making the above assertions and/or disregarding Applicant's comparative data of tests (a) and (b), the Examiner has confused suggested human dosages in the specification with doses given to mice in animal testing, and has improperly extended the patenting role of the US PTO into the safety and efficacy role of the FDA.[1]

Thus, the Examiner asserts that only 1.5 mg/kg of AZD2171 was tested, "but the specification teaches that an 'effective dose (as currently claimed) is 0.01-1.5 mg/kg (page 31); therefore, the full range of effective amount has not been tested." However, tests (a) and (b) were animal test models wherein the AZD2171 is administered to test *mice*, whereas the disclosure at page 31 of the specification cited by the Examiner states "for example approximately 0.03-1.5 mg/kg *in a human*. A unit does in the range, for example, 0.01-1.5mg/kg, preferably 0.03-0.5mg/kg is envisaged and this is *normally a therapeutically-effective dose*." The skilled persons responsible for designing and carrying out pre-clinical and clinical studies, which must

[1] It is believed that the further assertions made at page 8 of the Action, lines 5-13, that the comparative evidence is not commensurate in scope with the claims, have been obviated by the above amendments whereby the claims are now limited to the treatment of colorectal cancer (the type of cancer involved in the comparative tests), and alternative (c) in independent claims 15 and 16 (requiring combination therapy with both 5-FU and CPT-11) has been cancelled.

necessarily be conducted before FDA approval, are quite capable of taking the present disclosure and determining the appropriate dosage level. It is respectfully submitted that there is no basis in science or logic, or from the disclosure of the present application, to totally disregard the "significantly greater inhibition of tumour growth" observed in the mouse model with the combination of 3mg/kg dose of AZD2171 with 5-FU (Figure 1) and with CPU-11 (Figure 3) because it differs from the "normally" therapeutically-effective dose noted in the specification for a human.

Similarly, the Examiner's effective disqualification of test (b) as having no probative value because "only one dosage of CPT-11 is tested (25 mg/kg) relative to the specification disclosure that CPT-11 may be administered, "for example 350 mg/m^2 as an intravenous infusion," also disregards that test (b) was carried out in a mouse model whereas the statement, "for example CPT-11 may be dosed at $350mg/m^2$ as an intravenous infusion," is clearly a human dose level when viewed in context of this disclosure on specification page 31.

Thus, in effect the Examiner is requiring that the claims be limited to the particular dose levels and/or routes of administration of AZD2171 and the 5-FU or CPT-11 used with the mice in the animal model from which the comparative data was generated. In other words, the Examiner appears to be requiring Applicant to limit its composition claims to dose levels *suitable for experimental mice*. In practical effect, this would preclude Applicant from establishing patentability of its method of treatment claims by means of statistically significant data obtained using an art accepted animal model, and thus *require that Applicant conduct human clinical trials* in order to obtain a claim scope that would encompass human subjects.

It is respectfully submitted that such a requirement is **(1)** directly contrary to the Federal Circuit decision in *In re Brana*, 34 USPQ2d 1436 (Fed. Cir. 1995), which expressly sanctions the use of statistically significant data from art accepted animal models for purposes of patentability (as opposed to requiring human clinical data); **(2)** is contrary to the Federal Circuit decision in *In re Chupp*, 2 USPQ2d 1437 (Fed. Cir. 1987) that to overcome *prima facie* obviousness one need only show that the claimed composition possessed superior activity in one embodiment, and **(3)** is contrary to the well established principle that a valid claim may encompass inoperative species or embodiments, and in any event **(4)** the specification discloses appropriate dose ranges and

routes of administration for the components of the claimed composition in a manner sufficient to meet the enablement requirements of section 112.

(1) Acceptance of Animal Data for Patentability Purposes

The acceptance of animal data (as opposed to requiring clinical trials) *for patentability purposes* is made very clear in the Federal Circuit decision of *In re Brana*, 34 USPQ2d 1436 (Fed. Cir. 1995) (copy attached for the Examiner's convenience). Particular note should be taken from the following discussion t*hat the Federal Circuit took pragmatic approach in applying the tests and requirements for patentability*, recognizing the realities and timing faced by inventors trying to obtain meaningful patent coverage of pharmaceutical inventions. The Court specifically rejected the Commissioner's requirement, in effect, for Phase II human clinical data noting that the associated costs "would prevent many companies from obtaining patent protection on promising new inventions, thereby eliminating an incentive to pursue, through research and development, potential cures in many crucial areas such as the treatment of cancer" (34 USPQ2d at 1442-43; emphasis added).

The claims there in issue were directed toward compounds which were said to have "a better action and better action spectrum as anti-tumor substances" than previously published compounds. The previously published compounds had been screened for anti-tumor activity by testing their efficacy *in vivo* against two implanted leukemias in a mouse model. These *in vivo* tests were widely used by the National Cancer Institute to measure the anti-tumor properties of a compound. Applicant's specification, however, only illustrated the cytotoxicity of the claimed compounds against human tumor cells *in vitro*, and concluded that these tests "had a good action."

There initially was a rejection for *prima facie* obviousness under §103, which applicant rebutted by asserting unexpectedly better anti-tumor properties, including a declaration reporting tests *in vitro,* which were said to indicate that applicants' claimed compounds were far more effective as antitumor agents than the compounds disclosed in the prior art, using two specific types of human tumor cells. It is noteworthy that these animal tests were deemed sufficient to overcome the §103 rejection. However, the Examiner nevertheless issued a final rejection for non-enablement under §112, ¶ 1, asserting that (1) the specification failed to describe any specific disease against which the claimed compounds were active, and (2) the prior art tests of

the previous publication and the tests disclosed in the specification were not sufficient to establish a reasonable expectation that the claimed compounds had practical utility. Note that the final rejection, the Board affirmance thereof and the Federal Circuit decision all addressed the rejection *as a non-enablement rejection under §112.*

With respect to the examiner's second assertion in *Brana* (section 112 rejection), the Court noted that the initial burden of proof was on the Patent Office, and it held that here in the PTO had not met its initial burden. However, even if the PTO met its initial burden, the Court noted that applicants provided test results through a declaration, showing that several compounds within the scope of the claims exhibited significant antitumour activity against the L1210 standard tumor model *in vivo*, which "evidence alone should have been sufficient to satisfy applicants' burden" (34 USPQ2d at 1441-42). The Court continued:

> The Commissioner counters that such *in vivo* tests in animals are only preclinical tests to determine whether a compound is suitable for processing in the second stage of testing, by which he apparently means *in vivo* testing in humans, and therefore are not reasonably predictive of the success of the claimed compounds for treating cancer in humans. The Commissioner, as did the Board, confuses the requirements under the law for obtaining a patent with the requirements for obtaining government approval to market a particular drug for human consumption. See *Scott v. Finney*, 34 F.3d 1058, 1063, 32 USPQ2d 1115, 1120 (Fed.Cir. 1994) ("Testing for the full safety and efficacy of a prosthetic device is more properly left to the Food and Drug Administration (FDA). Title 35 does not demand that such human testing occur within the confines of Patent and Trademark Office (PTO) proceedings.").
>
> Our court's predecessor has determined that proof of an alleged pharmaceutical property for a compound by statistically significant tests with standard experimental animals is sufficient to establish utility. *In re Krimmel*, 292 F.2d 948, 953, 130 USPQ 215, 219 (CCPA 1961); see also *In re Bergel*, 292 F.2d 958, 130 USPQ 205 (CCPA 1961). In concluding that similar in *vivo tests* were adequate proof of utility the court in *In re Krimmel* stated:
>
> > We hold as we do because it is our firm conviction that one who has taught the public that a compound exhibits some desirable pharmaceutical property in a standard experimental animal has made a significant and useful contribution to the art, even though it may eventually appear that the compound is without value in the treatment of humans.
>
> *Krimmel*, 292 F.2d at 953, 130 USPQ at 219. Moreover, NCI apparently believes these tests are statistically significant because it has explicitly recognized both the P388 and L1210 murine tumor models as a standard screening test for determining whether new compounds may be useful as antitumour agents.

(34 USPQ2d at 1442; emphasis added).

The Commissioner cited two literature references (Martin and Pazdur) for the proposition that laboratory oncologists are skeptical about the predictive value of *in vivo* murine tumor models for human therapy. However, the Court dismissed this assertion, noting that even Martin recognizes that these tumor models continue to contribute to an increasing human cure rate. The Court then continued:

> On the basis of animal studies, and controlled testing in a limited number of humans (referred to as Phase I testing), the Food and Drug Administration may authorize Phase II clinical studies. See 21 U.S.C. Section 355(i)(1); 5 C.F.R. Section 312.23 (a)(5), (a)(8) (1994). Authorization for a Phase II study means that the drug may be administered to a larger number of humans, but still under strictly supervised conditions. The purpose of the Phase II study is to determine primarily the safety of the drug when administered to a larger human population, as well as its potential efficacy under different dosage regimes. See 21 C.F.R. Section 312.21(b).
> FDA approval, however, is not a prerequisite for finding a compound useful within the meaning of the patent laws. *Scott*, 34 F. 3d 1058, 1063, 32 USPQ2d 1115, 1120. Usefulness in patent law, and in particular in the context of pharmaceutical inventions, necessarily includes the expectation of further research and development. The stage at which an invention in this field becomes useful is well before it is ready to be administered to humans. Were we do require Phase II testing in order to prove utility the associated costs would prevent many companies from obtaining patent protection on promising new inventions, thereby eliminating an incentive to pursue, through research and development, potential cures in many crucial areas such as the treatment of cancer.
> In view of all of the foregoing, we conclude that applicants disclosure complies with the requirements of 35 U.S.C. Section 112 Para. 1.

(34 USPQ2d at 1442-43; emphasis added).

That the LS-174T colon cancer animal model is a standard or art accepted animal model is clearly indicated, *e.g.*, by the 56 document "hits" (ranging from 1986 to 2009) obtained April 5, 2010 when searching "(LS-174T AND xenograft*) AND (mice OR mouse OR murine) AND (nude OR athymic)" in the NCBI PubMed database.

In view of the above legal analysis, it is respectfully submitted that comparative data generated by the animal model described at pages 34-39 of the present specification, and graphically presented in Figures 1-4 presents sufficient statistically significant evidence of significantly greater inhibition of tumour grown from the combinations of AZD2171 with 5-FU and with CPU-11 to overcome any *prima facie* obviousness of the

present claims. Summarizing the statistical significance as noted on the respective figures:

Figure	Comparison	Significance
1	5-FU 50mg/kg vs 5-FU 50mg/kg + AZD2171 3mg/kg	$p<0.001$
1	AZD2171 3mg/kg vs. 5-FU 50mg/kg + AZD2171 3mg/kg	$p<0.05$
2	5-FU 50mg/kg vs 5-FU 50mg/kg + AZD2171 1.5mg/kg	$p<0.001$
2	AZD2171 1.5mg/kg vs. 5-FU 50mg/kg + AZD2171 1.5mg/kg	$p<0.4$
3	CPT-11 25mg/kg vs CPT-11 25mg/kg + AZD2171 3mg/kg	$p<0.001$
3	AZD2171 3mg/kg vs. CPT-11 25mg/kg + AZD2171 3mg/kg	$p<0.001$
4	CPT-11 25mg/kg vs CPT-11 25mg/kg + AZD2171 1.5mg/kg	$p<0.001$
4	AZD2171 1.5mg/kg vs. CPT-11 25mg/kg + AZD2171 1.5mg/kg	$p<0.05$

From the **test (a)** data graphically shown in Figures 1 and 2, the specification concludes at page 36:

> The combination of 5-FU with AZD2171 dosed at 3mg/kg produced a significantly greater inhibition of tumour growth than 5-FU alone or AZD2171 alone (Figure 1). The inhibition of tumour growth produced by the combination of the two agents AZD2171 and 5-FU was still greater than that produced by either agent alone when the dose of AZD2171 was reduced to 1.5mg/kg (Figure 2).

From the **test (b)** data graphically shown in Figures 3 and 42, the specification concludes at page 39:

> The combination of CPT-11 with AZD2171 dosed at 3mg/kg or 1.5mg/kg produced a significantly greater inhibition of tumour growth than CPT-11 alone or AZD2171 alone (Figures 3 and 4).

The current Patent Office Board of Appeals and Interferences has widely followed the pragmatic approach of the Federal Circuit (as it must). For example, the Board routinely cites and relies upon the holding of *In re Brana*

While *In re Brana* and the Board decisions discussing *Brana* are generally addressing non-enablement under section 112, the Board has recognized that the pragmatic approach of *Brana* with respect to the sufficiency of animal testing in pharmaceutical cases should be applied

to all patentability issues. Thus in *Ex parte Gregory*, Appeal 2008-005266 (BPAI 2009) (copy attached for the Examiner's convenience), the Board noted:

> Moreover, "[w]hen prima facie obviousness is established and evidence is submitted in rebuttal, the decision-maker must start over." *In re Rinehart*, 531 F.2d 1048, 1052 (CCPA 1976); *In re Hedges*, 783 F.2d 1038, 1039 (Fed. Cir. 1986) ("If a prima facie case is made in the first instance, and if the applicant comes forward with reasonable rebuttal, whether buttressed by experiment, prior art references, or argument, the entire merits of the matter are to be reweighed"). Thus, all of the evidence must be considered under the Graham factors in reaching the obviousness determination.
>
> In speaking about the relationship of patent law and FDA law, the Federal Circuit has noted:
>
> > On the basis of animal studies, and controlled testing in a limited number of humans (referred to as Phase I testing), the Food and Drug Administration may authorize Phase II clinical studies. See 21 U.S.C. § 355(i)(1); 5 C.F.R. § 312.23 (a)(5), (a)(8) (1994). Authorization for a Phase II study means that the drug may be administered to a larger number of humans, but still under strictly supervised conditions. The purpose of a Phase II study is to determine primarily the safety of the drug when administered to a larger human population, as well as its potential efficacy under different dosage regimens. See 21 C.F.R. § 312.21(b). FDA approval, however, is not a prerequisite for finding a compound useful within the meaning of the patent laws. . . . . Usefulness in patent law, and in particular the context of pharmaceutical inventions, necessarily includes the expectation of further research and development. The stage at which an invention in this field becomes useful is well before it is ready to be administered to humans. Were we to require Phase II testing in order to prove utility, the associated costs would prevent many companies from obtaining patent protection on promising new inventions, thereby eliminating an incentive to pursue, through research and development, potential cures in many crucial areas such as the treatment of cancer.
>
> *In re Brana*, 51 F.3d. 1560, 1568 (Fed. Cir. 1995) (citations omitted). Although the above statements were made in the context of utility and enablement, the clear inference is that FDA determinations are not controlling on patentability, which would include the obviousness determination.

(Ex parte Gregory at pages 8-10).[2]

[2] The facts of *In re Gregory* did not involve animal models. Rather, applicant was claiming a 300mg capsule of trimethobenzamide, which fell within the range of the 100mg, 200mg, 250mg and 400mg capsules previously approved by the FDA. The Board rejected applicant's assertion that FDA approval of its 300mg capsule demonstrated criticality sufficient to overcome *prima facie* obviousness.

It is therefore believed quite clear from the governing case law that patentability issues in the pharmaceutical arts, *whether utility, section 112 enablement or obviousness*, are not to be evaluated by FDA standards and human testing, but and that statistically significant results from accepted animal models are sufficient for all such patentability determinations. Accordingly, it is respectfully submitted that the Examiner's disregard of Applicants' animal test data for the reasons stated was in error, and this ground for rejection should be withdrawn.

(2) Comparative evidence to overcome *prima facie* obviousness one need only show that the claimed composition possessed superior activity in one embodiment

The facts before the Federal Circuit in *In re Chupp*, 2 USPQ2d 1437 (Fed. Cir. 1987) (copy attached for the Examiner's convenience) involved the US PTO rejection of claims to a certain chemical compound disclosed as herbicidal compositions to combat weeds in crops, as being *prima facie* obvious. Applicant submitted a declaration discussing the results of tests comparing the herbicidal activity of the claimed compound with that of the closest prior art compounds and with two commercial herbicides. The tests compared the compounds' ability to control two weeds, quackgrass and yellow nutsedge, in two crops, corn and soybeans. It was undisputed that the claimed compound gave significantly superior results. However, the Examiner maintained the rejection, saying that the comparative testing using only two weeds and two crops was insufficient to establish herbicidal activity. After a lengthy analysis of several prior decisions, the Federal Circuit concluded that "Chupp's evidence that the claimed compound possesses superior herbicidal activity on quackgrass and yellow nutsedge in corn and soybeans is sufficient to rebut the *prima facie* case of obviousness."

The Federal Circuit holding in *In re Chupp* has been specifically incorporated into MPEP ¶ 2145 for consideration of whether evidence is commensurate in scope with the claimed invention:

> When considering whether proffered evidence is commensurate in scope with the claimed invention, Office personnel should not require the applicant to show unexpected results over the entire range of properties possessed by a chemical compound or composition. See, e.g., *In re Chupp*, 816 F.2d 643, 646, 2 USPQ2d 1437, 1439 (Fed. Cir. 1987). Evidence that the compound or composition possesses superior and unexpected

> properties in one of a spectrum of common properties can be sufficient to rebut a *prima facie* case of obviousness. *Id.*
>
> For example, a showing of unexpected results for a single member of a claimed subgenus, or a narrow portion of a claimed range would be sufficient to rebut a *prima facie* case of obviousness if a skilled artisan "could ascertain a trend in the exemplified data that would allow him to reasonably extend the probative value thereof." *In re Clemens*, 622 F.2d 1029, 1036, 206 USPQ 289, 296 (CCPA 1980) (Evidence of the unobviousness of a broad range can be proven by a narrower range when one skilled in the art could ascertain a trend that would allow him to reasonably extend the probative value thereof.).

(MPEP ¶ 2145 (8th Ed., Rev. 6, Sept. 2007; emphasis added).

Similar to *Chupp* and consistent with the MPEP, Applicant in the present application has demonstrated significantly greater efficacy of the claimed combinations in a standard or accepted animal model and at different dose levels. Accordingly, this should be sufficient to overcome *prima facie* obviousness for the method of treatment as presently claimed.

(3) The Possibility That the Present Compound Claims May Encompass Inoperative Embodiments or Species Does Not Render Them Non-Enabled

The *In re Chupp* analysis as to whether claims are commensurate in scope with proffered evidence is also consistent with and supported by well established case law holding that a claim may encompass inoperative embodiments and still meet the enablement requirements. For Example, as recently stated by the Board in *Ex parte Eggenweiler.*, Appeal 2007-2495 (BPAI November 27, 2007) (copy attached for the Examiner's convenience):

> Second, the fact that "there is no known anticancer agent . . . effective against all cancers" is irrelevant. It is true of all known anticancer agents, and neither adds to nor detracts from the enablement of the instant derivatives. Finally, we know of no authority, and the Examiner cites none, that would require Appellants' imidazole derivatives to be "effective against all cancers" in order to support a claim directed to cancer treatment generally. On the contrary, a claim may encompass inoperative embodiments and still meet the enablement requirement of 35 U.S.C. § 112, first paragraph. See *Atlas Powder Co. v. E.I. Du Pont De Nemours & Co.*, 750 F.2d 1569, 1576, 224 USPQ 409, 413 (Fed. Cir. 1984), *In re Angstadt*, 537 F.2d 498, 504, 190

> USPQ 214, 218 (CCPA 1976), *In re Cook*, 439 F.2d 730, 732, 169 USPQ 298, 300 (CCPA 1971).

(Appeal 2007-2495 at page 5; emphasis added).

In the present application Applicant has submitted evidence demonstrating significantly greater efficacy of the claimed combinations in an accepted animal model and at different dose levels. There is no indication that this effect would not also be realized at other reasonable dosage levels and ratios within the guidance provided by the specification at pages 31-32, as discussed further below.

(4) The Specification Discloses Appropriate Dose Ranges and Routes of Administration for the Components of the Claimed Combination in a Manner Sufficient to Meet the Enablement Requirements of Section 112.

While the Examiner has not suggested that the present claims are not enabled, the Examiner has disregarded certain of Applicant's comparative evidence on the basis that the dose administered in the *mouse* model was outside of the dose range considered to be "therapeutically effective" in *humans*. Apart from the fact that the Examiner's argument would in effect improperly require human testing as discussed above, for completeness of the present analysis it is pointed out the skilled person is clearly enabled to determine appropriate human dose levels. Thus, at pages 31-32 the specification discloses dosage ranges within which AZD2171 would normally be administered. It further notes that 5-FU and CPT-11, being commercially available, may be dosed according to known routes of administration and dosages, and then provides alternative acceptable dosages and routes. Similar type dosage information in a specification has been found adequately enabling. For example, the following specification dose information was found enabling, to "adequately convey to any person skilled in the art useful daily dosage information for the claimed compounds" in *Ex parte Porubek*, Appeal No. 2001-1101 (BPAI, non precedential) (copy attached for the Examiner's convenience):

> While dosage values will vary, therapeutic compounds of the invention may be administered to a human subject requiring such treatment as an effective oral dose of about 50 mg to about 5000 mg per day, depending upon the weight of the patient. For any particular subject, specific dosage regimens should be adjusted to the individual's need and to the professional judgment of the person administering or supervising the administration of the inventive compounds.

(Appeal 2001-1101 at page 5).

The present disclosure with respect to dose ranges and routes of administration is far more informative, and it is respectfully submitted fully meets the requirements of the patent laws.

Information Disclosure Statement

The Examiner's attention is called to the further Information Disclosure Statement and form PTO-1449 being submitted herewith. It is respectfully requested that the Examiner consider the cited documents when this Application is next taken up for examination, and that this consideration be acknowledged on a copy of the form PTO-1449 returned to the undersigned.

Technically Related Pending Applications of Applicant's Assignee

The Examiner's attention is called to the following *updated* Table of pending U.S. applications of Applicants' assignee which might be considered technically related, each of which claims a combination of AZD2171 with another therapeutic agent identified under the heading "Combination." The current status of each application as reported in the PAIR database is given in the right-hand column. Each recently published US application on the below updated table is listed on the form PTO-1449 attached to the Information Disclosure Statement being submitted herewith. All other documents have been previously listed and copies provided in this application.

It is assumed that the Examiner has ready electronic access to each of the pending US applications, but the undersigned will provide a copy of any document from these files if requested by the Examiner.

U.S. Serial No. Filing Date	First Named Inventor	U.S. Pub. No. U.S. Pub. Date	PCT Pub. No. PCT Pub. Date	Combination With	Current Status
10/240,413 October 1, 2002	Jon Curwen et al.	US 20030144298 July 31, 2003	WO 01/74360 October 11, 2001	Anti-hypertensive	Pending before Examiner Sharmila Gollamudi Landau in GAU 1611; Response to Non Final Action Filed 12-23-2009.
10/555,389 November 3, 2005	Jon Curwen et al.	US 20060223815 October 5, 2006	WO 2004/098604 November 18, 2004	Anti-angiogenic agent + src inhibitor	Abandoned; continued

U.S. Serial No. Filing Date	First Named Inventor	U.S. Pub. No. U.S. Pub. Date	PCT Pub. No. PCT Pub. Date	Combination With	Current Status
12/568,643 September 28, 2009	Jon Curwen et al.	US 20100029673 February 4, 2010	WO 2004/098604 November 18, 2004	Anti-angiogenic agent + src inhibitor	Application Undergoing Preexam Processing
10/563,440 January 5, 2006	Stephen Wedge	US 20060160775 July 20, 2006	WO 2005/004871 January 20, 2005	ZD6126	Abandoned
10/563,439 January 5, 2006	Stephen Wedge	US 20060167024 July 27, 2006	WO 2005/004872 January 20, 2005	ZD1839	Abandoned; continued
12/555,592 September 8, 2009	Stephen Wedge		WO 2005/004872 January 20, 2005	ZD1839	Application Undergoing Preexam Processing
10/594,235 September 25, 2006	Stephen Wedge	US 20080113039 May 15, 2008	WO 2005/092384 October 6, 2005	Platinum anti-tumor agent, optionally IR	Assigned to Examiner Kyle A Purdy in GAU 1611; Final Rejection Mailed 12-22-2009
10/594,234 September 25, 2006	Stephen Wedge	US 20070135462 June 14, 2007	WO 2005/092385 October 6, 2005	Taxane. optionally IR	Assigned to Examiner Rachael E Welter in GAU 1611; Final Rejection Mailed 03-31-2010
11/663,912 March 27, 2007	Stephen Wedge	US 20080015205 January 17, 2008	WO 2006/035203 April 6, 2006	Imatinib [Gleevec]	Abandoned; continued
12/408,833 March 23, 2009	Stephen Wedge	US 20090325977 December 31, 2009	WO 2006/035203 April 6, 2006	Imatinib [Gleevec]	Assigned to Examiner James D. Anderson in GAU 1614; Non Final Action Mailed 04-15-2010
11/994,824 August 15, 2008	Stephen Wedge	US 20090176731 July 9, 2009	WO 2007/003933 January 11, 2007	Gemcitabane [Gemzar]	Assigned to Examiner Anna Pagonakis in GAU 1628; Non Final Action Mailed 03-23-2010
12/158,266 June 19, 2008	Stephen Wedge	US 20080306094 December 11, 2008	WO 2007/071970 June 28, 2007	pemetrexed	Assigned to Examiner Anna Pagonakis in GAU 1628; Final Rejection Mailed 03-12-2010
12/097,384 June 13, 2008	David Blakey et al.	US 20090123474 May 14, 2009	WO 2007/068895 June 21, 2007	Angiopoietin-2 antagonist and antagonist of VEGF-A, and/or KDR, and/or Flt1	Assigned to Examiner Phuong N Huynh in GAU 1644; Response to Restriction Requirement Filed 04-13-2010
12/595,746 January 4, 2010	Stephen Wedge		WO 2008/125820 October 23, 2008	MEK Inhibitors	Application Undergoing Preexam Processing

The Examiner's attention is also called to the following *updated* Table listing technically related pending U.S. applications of Applicant's assignee that claim a combination of 5-FU and/or CPT-11 with another therapeutic agent identified under the heading "Combination with." The current status of these applications as reported in the PAIR database is given in the right-hand column. The published US applications and PCT application were previously cited in this application and a copy of the published PCT application was previously provided.

Again, it is assumed that the Examiner has ready electronic access to this pending US application, but the undersigned will provide a copy of any document from these files if requested by the Examiner.

U.S. Serial No. Filing Date	First Named Inventor	U.S. Pub. No. U.S. Pub. Date	PCT Pub. No. PCT Pub. Date	Combination With	Current Status
10/543,106 July 22, 2005	Stephen Wedge	US 20060142316 June 29, 2006	WO 2004/071397 August 26, 2004	ZD6474	Abandoned; continued
12/501,599 July 13, 2009	Stephen Wedge		WO 2004/071397 August 26, 2004	ZD6474	Assigned to Examiner Christopher Stone in GAU 1614; Non Final Action Mailed 04-09-2010

EXCEPT for issue fees payable under 37 C.F.R. § 1.18, the Director is hereby authorized by this paper to charge any additional fees during the entire pendency of this application including fees due under 37 C.F.R. §§ 1.16 and 1.17 which may be required, including any required extension of time fees, or credit any overpayment to Deposit Account 50-0310. This paragraph is intended to be a **CONSTRUCTIVE PETITION FOR EXTENSION OF TIME** in accordance with 37 C.F.R. § 1.136(a)(3).

Respectfully Submitted,
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Source: USPQ, 2d Series (1986 - Present) > U.S. Court of Appeals, Federal Circuit > In re Brana, 34 USPQ2d 1436 (Fed. Cir. 1995)

In re Brana, 34 USPQ2d 1436 (Fed. Cir. 1995)

34 USPQ2d 1436
In re Brana
U.S. Court of Appeals Federal Circuit
No. 93-1393
Decided March 30, 1995
51 F3d 1560

Headnotes

PATENTS

[1] Patentability/Validity -- Utility (▶ 115.10)

Patentability/Validity -- Specification -- Enablement (▶ 115.1105)

Application for pharmaceutical invention did not fail to disclose specific disease against which claimed compounds are useful, and thereby fail to satisfy enablement requirement of 35 USC 112, since specification, which favorably compares compounds of invention with known compounds found to be highly effective against lymphocytic leukemia tumor models, implicitly asserts that claimed compounds are also highly effective against those models, and since tumor models are cell lines representing specific lymphocytic tumors.

[2] Patentability/Validity -- Utility (▶ 115.10)

Patentability/Validity -- Specification -- Enablement (▶ 115.1105)

Patent and Trademark Office improperly rejected, for lack of utility, application claims for pharmaceutical compounds used in cancer treatment in humans, since neither nature of invention nor evidence proferred by PTO would cause one of ordinary skill in art to reasonably doubt asserted utility, and since even if utility of compounds could be reasonably questioned, evidence that compounds within scope of claims, and other structurally similar compounds, are effective as chemotherapeutic agents in animals would be sufficient to convince one skilled in art of asserted utility; absence of evidence that claimed compounds have chemotherapeutic effect in humans does not warrant contrary conclusion, since proof of alleged pharmaceutical property for compound by statistically significant tests using standard experimental animals is sufficient to establish utility.

Case History and Disposition

Appeal from the U.S. Patent and Trademark Office, Board of Patent Appeals and Interferences.

Patent application of Miguel F. Brana, Jose M.C. Berlanga, Marina M. Moset, Erich Schlick and Gerhard Keilhauer, serial no. 07/533,944, filed June 4, 1990, which is a continuation of serial no. 213,690, filed June 30, 1988. From decision upholding examiner's rejection of claims 10-13, applicants appeal.

Reversed.

Attorneys

Malcolm J. MacDonald, Herbert B. Keil, and David S. Nagy, Washington, D.C., for appellants.

Fred E. McKelvey, Solicitor, PTO; Albin F. Drost, Deputy Solicitor; Richard E. Schafer, Teddy S. Gron, Joseph G. Piccolo and Richard L. Torczon, Associate Solicitors, for appellee.

Judge

Before Plager, Lourie, and Rader, circuit judges.

Opinion Text

Opinion By:

Plager, J.

Miguel F. Brana, *et al.* (applicants), appeal the March 19, 1993 decision of the United States Patent and Trademark Office (PTO) Board of Patent Appeals and Interferences (Board), in Appeal No. 92-1196. The Board *affirmed* the examiner's rejection of claims 10-13 of patent application Serial No. 533,944 under 35 U.S.C. Section 112 Para.1 (1988). [1]The examiner's rejection, upon which the Board relied in rendering its decision, was based specifically on a challenge to the utility of the claimed compounds and the amount of experimentation necessary to use the compounds. We conclude the Board erred, and reverse.

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[1] Unless otherwise noted, all United States Code citations are to the 1988 edition.

I. BACKGROUND

On June 30, 1988, applicants filed patent application Serial No. 213,690 (the '690 application) [2] directed to 5-nitrobenzo [de]isoquinoline-1,3-dione compounds, for use as antitumor substances, having the following formula:

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[2] This is a divisional of patent application Serial No. 110,871 filed October 21, 1987.

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where n is 1 or 2, R^1 and R^2 are identical or different and are each hydrogen,

C1-C6-alkyl, C1-C6-hydroxyalkyl, pyrrolidinyl, morpholino, piperidinyl or piperacinyl, and R^3 and R^4 are identical or different and are each hydrogen, C1-C6-alkyl, C1-C6-acyl, C2-C7-alkoxycarbonyl, ureyl, aminocarbonyl or C2-C7-alkylaminocarbonyl. These claimed compounds differ from several prior art

benzo [de]isoquinoline-1,3-dione compounds due to the presence of a nitro group (O2N) at the 5-position and an amino or other amino group (NR ^{3}R ^{4}) at the 8-position of the isoquinoline ring.

The specification states that these non- symmetrical substitutions at the 5- and 8-positions produce compounds with "a better action and a better action spectrum as antitumor substances" than known benzo [de]isoquinolines, namely those in K.D. Paull et al., *Computer Assisted Structure- Activity Correlations, Drug Research, 34(II),* 1243-46 (1984) (Paull). Paull describes a computer-assisted evaluation of benzo [de]isoquinoline-1,3-diones and related compounds which have been screened for antitumor activity by testing their efficacy *in vivo* [3] against two specific implanted murine (i.e., utilizing mice as test subjects) lymphocytic leukemias, P388 and L1210. [4]These two *in vivo* tests are widely used by the National Cancer Institute (NCI) to measure the antitumor properties of a compound. Paull noted that one compound in particular, benzo [de]isoquinoline-1,3(2H)dione,5-amino-2(2-dimethyl-aminoethyl [sic]) (hereinafter "NSC 308847"), was found to show excellent activity against these two specific tumor models. Based on their analysis, compound NSC 308847 was selected for further studies by NCI. In addition to comparing the effectiveness of the claimed compounds with structurally similar compounds in Paull, applicants' patent specification illustrates the cytotoxicity of the claimed compounds against human tumor cells, *in vitro,* [5]and concludes that these tests "had a good action." [6]

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[3] *In vivo* means " [i]n the living body, referring to a process occurring therein." *Steadman's Medical Dictionary* 798 (25th ed. 1990). *In vitro* means " [i]n an artificial environment, referring to a process or reaction occurring therein, as in a test tube or culture media." *Id.*

[4] The analysis in Paull consisted of grouping the previously-tested compounds into groups based on common structural features and cross- referencing the various groups, in light of the success rates of the group as a whole, to determine specific compounds that may be effective in treating tumors.

[5] *See supra* note 3.

[6] The specification does not state the specific type of human tumor cells used in this test.

The examiner initially rejected applicants' claims in the '690 application as obvious under 35 U.S.C. Section 103 in light of U.S. Patent No. 4,614,820, issued to and referred to hereafter as Zee-Cheng *et al.* Zee-Cheng *et al.* discloses a benzo [de]isoquinoline compound for use as an antitumor agent with symmetrical substitutions on the 5-position and 8-position of the quinoline ring; in both positions the substitution was either an amino or nitro group. [7]Although not identical to the applicants' claimed compounds, the examiner noted the similar substitution pattern (i.e., at the same positions on the isoquinoline ring) and concluded that a mixed substitution of the invention therefore would have been obvious in view of Zee-Cheng *et al.*

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[7] The chemical compound in Zee-Cheng *et al.* is labeled a 3,6-disubstituted-1,8-naphthalimide and uses different numbering for the positions on the isoquinoline ring. The structure of this compound, however, is identical to that claimed by the applicants except for symmetrical substitutions at the 5-position and the 8-position of the isoquinoline ring. Zee-Cheng *et al.* teaches identical substitutions of amino or nitro groups while applicants claim a nitro group substitution at the 5-position and an amino group substitution at the 8-position.

In a response dated July 14, 1989, the applicants rebutted the Section 103 rejection. Applicants asserted that their mixed disubstituted compounds had unexpectedly better antitumor properties than the

symmetrically substituted compounds in Zee-Cheng *et al.* In support of this assertion applicants attached the declaration of Dr. Gerhard Keilhauer. In his declaration Dr. Keilhauer reported that his tests indicated that applicants' claimed compounds were far more effective as antitumor agents than the compounds disclosed in Zee-Cheng *et al.* when tested, *in vitro,* against two specific types of human tumor cells, HEp and HCT-29. [8]Applicants further noted that, although the differences between the compounds in Zee-Cheng *et al.* and applicants' claimed compounds were slight, there was no suggestion in the art that these improved results (over Zee-Cheng *et al.*) would have been expected. Although the applicants overcame the Section 103 rejection, the examiner nevertheless issued a final rejection, on different grounds, on September 5, 1989.

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[8] HEp cells are derived from laryngeal cancer and HCT-29 cells from colon cancer.

On June 4, 1990, applicants filed a continuation application, Serial No. 533,944 (the '944 application), from the above-mentioned '690 application. Claims 10-13, the only claims remaining in the continuation application, were rejected in a final office action dated May 1, 1991. Applicants appealed the examiner's final rejection to the Board.

In his answer to the applicants' appeal brief, the examiner stated that the final rejection was based on 35 U.S.C. Section 112 Para.1. [9]The examiner first noted that the specification failed to describe any specific disease against which the claimed compounds were active. Furthermore, the examiner concluded that the prior art tests performed in Paull and the tests disclosed in the specification were not sufficient to establish a reasonable expectation that the claimed compounds had a practical utility (i.e. antitumor activity in humans). [10]

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[9] The examiner's answer noted that the final rejection also could have been made under 35 U.S.C. Section 101 for failure to disclose a practical utility.

[10] The examiner subsequently filed two supplemental answers in response to arguments raised by the applicants in supplemental reply briefs.

In a decision dated March 19, 1993, the Board *affirmed* the examiner's final rejection. The three-page opinion, which lacked any additional analysis, relied entirely on the examiner's reasoning. Although noting that it also would have been proper for the examiner to reject the claims under 35 U.S.C. Section 101, the Board *affirmed* solely on the basis of the Examiner's Section 112 Para.1 rejection. This appeal followed.

II. DISCUSSION

At issue in this case is an important question of the legal constraints on patent office examination practice and policy. The question is, with regard to pharmaceutical inventions, what must the applicant prove regarding the practical utility or usefulness of the invention for which patent protection is sought. This is not a new issue; it is one which we would have thought had been settled by case law years ago. [11]We note the Commissioner has recently addressed this question in his Examiner Guidelines for Biotech Applications, *see* 60 Fed.Reg. 97 (1995); 49 Pat. Trademark & Copyright J. (BNA) No. 1210, at 234 (Jan. 5, 1995).

[11] *See, e.g., Cross v. Iizuka,* 753 F.2d 1040, 224 USPQ 739 (Fed.Cir. 1985); *In re Langer,* 503 F.2d 1380, 183 USPQ 288 (CCPA 1974); *In re Krimmel,* 292 F.2d 948, 130 USPQ 215 (CCPA 1961); *In re Bergel,* 292 F.2d 958, 130 USPQ 205 (CCPA 1961).

The requirement that an invention have utility is found in 35 U.S.C. Section 101: "Whoever invents . . . any new and *useful* . . . composition of matter . . . may obtain a patent therefor. . . ." (emphasis added). It is also implicit in Section 112 Para.1, which reads:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same, and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Obviously, if a claimed invention does not have utility, the specification cannot enable one to use it.

As noted, although the examiner and the Board both mentioned Section 101, and the rejection appears to be based on the issue of whether the compounds had a practical utility, a Section 101 issue, the rejection according to the Board stands on the requirements of Section 112 Para.1. It is to that provision that we address ourselves. [12] The Board gives two reasons for the rejection; [13]we will consider these in turn.

[12] This court's predecessor has determined that absence of utility can be the basis of a rejection under both 35 U.S.C. Section 101 and Section 112 Para.1. *In re Jolles,* 628 F.2d 1322, 1326 n.11, 206 USPQ 885, 889 n.11 (CCPA 1980); *In re Fouche,* 439 F.2d 1237, 1243, 169 USPQ 429, 434 (CCPA 1971) (" [I]f such compositions are in fact useless, appellant's specification cannot have taught how to use them."). Since the Board *affirmed* the examiner's rejection based solely on Section 112 Para.1, however, our review is limited only to whether the application complies with Section 112 Para.1.

[13] The Board's decision did not expressly make any independent factual determinations or legal conclusions. Rather, the Board stated that it "agree [d] with the examiner's well reasoned, well stated and fully supported by citation of relevant precedent position in every particular, and any further comment which we might add would be redundant." *Ex parte Brana et al.* , No. 92-1196 (Bd. Pat. App. & Int. March 19, 1993) at 2-3. Therefore, reference in this opinion to Board findings are actually arguments made by the examiner which have been expressly adopted by the Board.

1.

The first basis for the Board's decision was that the applicants' specification failed to disclose a specific disease against which the

claimed compounds are useful, and therefore, absent undue experimentation, one of ordinary skill in the art was precluded from using the invention. *See Hybritech Inc. v. Monoclonal Antibodies, Inc.* , 802 F.2d 1367, 1384, 231 USPQ 81, 94 (Fed.Cir. 1986), cert. denied, 480 U.S. 947 (1987). In support, the Commissioner argues that the disclosed uses in the '944 application, namely the "treatment of diseases" and "antitumor substances," are similar to the nebulous disclosure found insufficient in *In re Kirk,* 376 F.2d 936, 153 USPQ 48 (CCPA 1967). This argument is not without merit.

In *Kirk* applicants claimed a new class of steroid compounds. One of the alleged utilities disclosed in the specification was that these compounds possessed "high biological activity." *Id.* at 938, 153 USPQ at 50. The specification, however, failed to disclose which biological properties made the compounds useful. Moreover, the court found that known specific uses of similar compounds did not cure this defect since there was no disclosure in the specification that the properties of the claimed compounds were the same as those of the known similar compounds. *Id.* at 942, 153 USPQ at 53. Furthermore, it was not alleged that one of skill in the art would have known of any specific uses, and therefore, the court concluded this alleged use was too obscure to enable one of skill in the art to use the claimed invention. *See also Kawai v. Metlesics,* 480 F.2d 880, 178 USPQ 158 (CCPA 1973).

[1] *Kirk* would potentially be dispositive of this case were the above-mentioned language the only assertion of utility found in the '944 application. Applicants' specification, however, also states that the claimed compounds have "a better action and a better action spectrum as antitumor substances" than known compounds, specifically those analyzed in Paull. As previously noted, *see supra* note 4, Paull grouped various benzo [de]isoquinoline-1,3-diones, which had previously been tested *in vivo* for antitumor activity against two lymphocytic leukemia tumor models (P388 and L1210), into various structural classifications and analyzed the test results of the groups (i.e. what percent of the compounds in the particular group showed success against the tumor models). Since one of the tested compounds, NSC 308847, was found to be highly effective against these two lymphocytic leukemia tumor models, [14]applicants' favorable comparison implicitly asserts that their claimed compounds are highly effective (i.e. useful) against lymphocytic leukemia. An alleged use against this particular type of cancer is much more specific than the vaguely intimated uses rejected by the courts in *Kirk* and *Kawai. See, e.g., Cross v. Iizuka,* 753 F.2d at 1048, 224 USPQ at 745 (finding the disclosed practical utility for the claimed compounds -- the inhibition of thromboxane synthetase in human or bovine platelet microsomes -- sufficiently specific to satisfy the threshold requirement in *Kirk* and *Kawai.*)

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[14] Paull also found NSC 308847 to be effective against two other test models, B16 melanoma and Colon C872.

The Commissioner contends, however, that P388 and L1210 are not diseases since the only way an animal can get sick from P388 is by a direct injection of the cell line. The Commissioner therefore concludes that applicants' reference to Paull in their specification does not provide a specific disease against which the claimed compounds can be used. We disagree.

As applicants point out, the P388 and L1210 cell lines, though technically labeled tumor models, were originally derived from lymphocytic leukemias in mice. Therefore, the P388 and L1210 cell lines do represent actual specific lymphocytic tumors; these models will produce this particular disease once implanted in mice. If applicants were required to wait until an animal naturally developed this specific tumor before testing the effectiveness of a compound against the tumor *in vivo,* as would be implied from the Commissioner's argument, there would be no effective way to test compounds *in vivo* on a large scale.

We conclude that these tumor models represent a specific disease against which the claimed compounds are alleged to be effective. Accordingly, in light of the explicit reference to Paull, applicants' specification alleges a sufficiently specific use.

2.

The second basis for the Board's rejection was that, even if the specification did allege a specific use, applicants failed to prove that the claimed compounds are useful. Citing various references, [15]the Board found, and the Commissioner now argues, that the tests offered by the applicants to prove utility

were inadequate to convince one of ordinary skill in the art that the claimed compounds are useful as antitumor agents. [16]

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[15] *See* Pazdur et al., *Correlation of Murine Antitumor Models in Predicting Clinical Drug Activity in Non-Small Cell Lung Cancer: A Six Year Experience,* 3 *Proceedings Am. Soc. Clin. Oncology* 219 (1984); Martin et al., *Role of Murine Tumor Models in Cancer Research,* 46 *Cancer Research* 2189 (April 1986).

[16] As noted, this would appear to be a Section 101 issue, rather than Section 112.

This court's predecessor has stated:

> [A] specification disclosure which contains a teaching of the manner and process of making and using the invention in terms which correspond in scope to those used in describing and defining the subject matter sought to be patented *must* be taken as in compliance with the enabling requirement of the first paragraph of Section 112 *unless* there is reason to doubt the objective truth of the statements contained therein which must be relied on for enabling support.

In re Marzocchi, 439 F.2d 220, 223, 169 USPQ 367, 369 (CCPA 1971). From this it follows that the PTO has the initial burden of challenging a presumptively correct assertion of utility in the disclosure. *Id.* at 224, 169 USPQ at 370. Only after the PTO provides evidence showing that one of ordinary skill in the art would reasonably doubt the asserted utility does the burden shift to the applicant to provide rebuttal evidence sufficient to convince such a person of the invention's asserted utility. *See In re Bundy,* 642 F.2d 430, 433, 209 USPQ 48, 51 (CCPA 1981). [17]

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[17] *See also In re Novak,* 306 F.2d 924, 928, 134 USPQ 335, 337 (CCPA 1962) (stating that it is proper for the examiner to request evidence to substantiate an asserted utility unless one with ordinary skill in the art would accept the allegations as obviously valid and correct); *In re Chilowsky,* 229 F.2d 457, 462, 108 USPQ 321, 325 (CCPA 1956) (" [W]here the mode of operation alleged can be readily understood and conforms to the known laws of physics and chemistry . . . no further evidence is required."). *But see In re Marzocchi,* 439 F.2d at 223, 169 USPQ at 369-70 ("In the field of chemistry generally there may be times when the well-known unpredictability of chemical reactions will alone be enough to create a reasonable doubt as to the accuracy of a particular broad statement put forward as enabling support for a claim. This will especially be the case where the statement is, on its face, contrary to generally accepted scientific principles.").

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[2] The PTO has not met this initial burden. The references cited by the Board, Pazdur and Martin, [18]do not question the usefulness of any compound as an antitumor agent or provide any other evidence to cause one of skill in the art to question the asserted utility of applicants' compounds. Rather, these references merely discuss the therapeutic predictive value of *in vivo* murine tests -- relevant only if applicants must prove the ultimate value in humans of their asserted utility. Likewise, we do not find that the nature of applicants' invention alone would cause one of skill in the art to reasonably doubt the asserted usefulness.

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[18] *See supra* note 15.

The purpose of treating cancer with chemical compounds does not suggest an inherently unbelievable undertaking or involve implausible scientific principles. *In re Jolles,* 628 F.2d at 1327, 206 USPQ at 890. Modern science has previously identified numerous successful chemotherapeutic agents. In addition, the prior art, specifically Zee Cheng *et al.* , discloses structurally similar compounds to those claimed by the applicants which have been proven *in vivo* to be effective as chemotherapeutic agents against various tumor models.

Taking these facts -- the nature of the invention and the PTO's proffered evidence -- into consideration we conclude that one skilled in the art would be without basis to reasonably doubt applicants' asserted utility on its face. The PTO thus has not satisfied its initial burden. Accordingly, applicants should not have been required to substantiate their presumptively correct disclosure to avoid a rejection under the first paragraph of Section 112. *See In re Marzocchi,* 439 F.2d at 224, 169 USPQ at 370.

We do not rest our decision there, however. Even if one skilled in the art would have reasonably questioned the asserted utility, i.e., even if the PTO met its initial burden thereby shifting the burden to the applicants to offer rebuttal evidence, applicants proffered sufficient evidence to convince one of skill in the art of the asserted utility. In particular, applicants provided through Dr. Kluge's declaration [19] test results showing that several compounds within the scope of the claims exhibited significant antitumor activity against the L1210 standard tumor

model *in vivo*. Such evidence alone should have been sufficient to satisfy applicants' burden.

[19] The declaration of Michael Kluge was signed and dated June 19, 1991. This declaration listed test results (i.e. antitumor activity) of the claimed compounds, *in vivo,* against L1210 tumor cells and concluded that these compounds would likely be clinically useful as anti-cancer agents. Enablement, or utility, is determined as of the application filing date. *In re Glass,* 492 F.2d 1228, 1232, 181 USPQ 31, 34 (CCPA 1974). The Kluge declaration, though dated after applicants' filing date, can be used to substantiate any doubts as to the asserted utility since this pertains to the accuracy of a statement already in the specification. *In re Marzocchi,* 439 F.2d at 224 n.4, 169 USPQ at 370 n.4. It does not render an insufficient disclosure enabling, but instead goes to prove that the disclosure was in fact enabling when filed (i.e., demonstrated utility).

The prior art further supports the conclusion that one skilled in the art would be convinced of the applicants' asserted utility. As previously mentioned, prior art -- Zee Cheng *et al.* and Paull -- disclosed structurally similar compounds which were proven *in vivo* against various tumor models to be effective as chemotherapeutic agents. Although it is true that minor changes in chemical compounds can radically alter their effects on the human body, *Kawai,* 480 F.2d at 891, 178 USPQ at 167, evidence of success in structurally similar compounds is relevant in determining whether one skilled in the art would believe an asserted utility. *See Rey-Bellet v. Engelhardt,* 493 F.2d 1380, 181 USPQ 453 (CCPA 1974); *Kawai,* 480 F.2d 880, 178 USPQ 158 .

The Commissioner counters that such *in vivo* tests in animals are only preclinical tests to determine whether a compound is suitable for processing in the second stage of testing, by which he apparently means *in vivo* testing in humans, and therefore are not reasonably predictive of the success of the claimed compounds for treating cancer in humans. [20]The Commissioner, as did the Board, confuses the requirements under the law for obtaining a patent with the requirements for obtaining government approval to market a particular drug for human consumption. *See Scott v. Finney,* 34 F.3d 1058, 1063,

32 USPQ2d 1115, 1120 (Fed.Cir. 1994) ("Testing for the full safety and effectiveness of a prosthetic device is more properly left to the Food and Drug Administration (FDA). Title 35 does not demand that such human testing occur within the confines of Patent and Trademark Office (PTO) proceedings.").

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[20] We note that this discussion is relevant to the earlier discussion as well. If we were to conclude that these *in vivo* tests are insufficient to establish usefulness for the claimed compounds, that would bear on the issue of whether one skilled in the art would, in light of the structurally similar compounds in Paull and Zee Cheng *et al.* , have cause to doubt applicants' asserted usefulness for the compounds.

Our court's predecessor has determined that proof of an alleged pharmaceutical property for a compound by statistically significant tests with standard experimental animals is sufficient to establish utility. *In re Krimmel,* 292 F.2d 948, 953, 130 USPQ 215, 219 (CCPA 1961); *see also In re Bergel,* 292 F.2d 958, 130 USPQ 205 (CCPA 1961). In concluding that similar *in vivo* tests were adequate proof of utility the court in *In re Krimmel* stated:

> We hold as we do because it is our firm conviction that one who has taught the public that a compound exhibits some desirable pharmaceutical property in a standard experimental animal has made a significant and useful contribution to the art, even though it may eventually appear that the compound is without value in the treatment of humans.

Krimmel, 292 F.2d at 953, 130 USPQ at 219. Moreover, NCI apparently believes these tests are statistically significant because it has explicitly recognized both the P388 and L1210 murine tumor models as standard screening tests for determining whether new compounds may be useful as antitumor agents.

In the context of this case the Martin and Pazdur references, on which the Commissioner relies, do not convince us otherwise. Pazdur only questions the reliability of the screening tests against lung cancer; it says nothing regarding other types of tumors. Although the Martin reference does note that some laboratory oncologists are skeptical about the predictive value of *in vivo* murine tumor models for human therapy, Martin recognizes that these tumor models continue to contribute to an increasing human cure rate. In fact, the authors conclude that this perception (i.e. lack of predictive reliability) is not tenable in light of present information.

On the basis of animal studies, and controlled testing in a limited number of humans (referred to as Phase I testing), the Food and Drug Administration may authorize Phase II clinical studies. *See* 21 U.S.C. Section 355(i)(1); 5 C.F.R. Section 312.23 (a)(5), (a)(8) (1994). Authorization for a Phase II study means that the drug may be administered to a larger number of humans, but still under strictly supervised conditions. The purpose of the Phase II study is to determine primarily the safety of the drug when administered to a larger human population, as well as its potential efficacy under different dosage regimes. *See* 21 C.F.R. Section 312.21(b).

FDA approval, however, is not a prerequisite for finding a compound useful within the meaning of the patent laws. *Scott,* 34 F.3d 1058, 1063, 32 USPQ2d 1115, 1120. Usefulness in patent law, and in particular in the context of pharmaceutical inventions, necessarily includes the expectation of further research and development. The stage at which an invention in this field becomes useful is well before it is ready to be administered to humans. Were we to require Phase II testing in order to prove utility, the

associated costs would prevent many companies from obtaining patent protection on promising new inventions, thereby eliminating an incentive to pursue, through research and development, potential cures in many crucial areas such as the treatment of cancer.

In view of all the foregoing, we conclude that applicants' disclosure complies with the requirements of 35 U.S.C. Section 112 Para.1.

3.

The Commissioner takes this opportunity to raise the question of this court's standard of review when deciding cases on appeal from the PTO. Traditionally we have recited our standard of review to be, with regard to questions of law, that review is without deference to the views of the Agency, *In re Donald son,* 16 F.3d 1189, 1192, 29 USPQ2d 1845, 1848 (Fed.Cir. 1994) (in banc), *In re Caveney,* 761 F.2d 671, 674, 226 USPQ 1, 3 (Fed.Cir. 1985), and with regard to questions of fact, we defer to the Agency unless its findings are "clearly erroneous." *See, e.g., In re Baxter Travenol Labs,* 952 F.2d 388, 21 USPQ2d 1281 (Fed.Cir. 1991); *In re Woodruff,* 919 F.2d 1575, 16 USPQ2d 1934 (Fed.Cir. 1990); *In re De Blauwe,* 736 F.2d 699, 222 USPQ 191 (Fed.Cir. 1984).

With regard to judgment calls, those questions that fall " [s]omewhere near the middle of the fact-law spectrum," this court has recognized "the falseness of the fact-law dichotomy, since the determination at issue, involving as it does the application of a general legal standard to particular facts, is probably most realistically described as neither of fact nor law, but mixed." *Campbell v. Merit Systems Protection Board,* 27 F.3d 1560, 1565 (Fed.Cir. 1994). When these questions of judgment are before us, whether we defer, and the extent to which we defer, turns on the nature of the case and the nature of the judgment. *Id.* ("Characterization therefore must follow from an *a priori* decision as to whether deferring . . . is sound judicial policy. We would be less than candid to suggest otherwise.").

The Commissioner contends that the appropriate standard of review for this court regarding questions of law, of fact, and mixed questions of law and fact, coming to us from the PTO is found in the Administrative Procedure Act (APA) at 5 U.S.C. Section 706. The standard set out there is that " [t]he reviewing court shall . . . hold unlawful and set aside agency action, findings, and conclusions found to be -- (A) arbitrary, capricious, an abuse of discretion, or otherwise not in accordance with law; . . . (E) unsupported by substantial evidence. . . ." The Commissioner is of the view that the stated standard we now use, which is the traditional standard of review for matters coming from a trial court, is not appropriate for decisions coming from an agency with presumed expertise in the subject area, and is not in accord with law. [21]

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[21] Congress enacted the Administrative Procedure Act (APA) on June 11, 1946. *See* 1 *Kenneth Culp Davis, Administrative Law Treatise,* Section 1:7 (2d ed. 1978). The APA sets forth a framework for administrative agency procedure and provides judicial review for persons adversely affected by final agency actions. Chapter 7, codified at 5 U.S.C. Sections 701-706, contains the APA judicial review provisions, including the standard of review provision quoted above.

Applicants argue that by custom and tradition, recognized by the law of this court, the standard of review we have applied, even though inconsistent with the standard set forth in the APA, nevertheless is a permissible standard. In our consideration of this issue, there is a reality check: would it matter to the outcome in a given case which formulation of the standard a court articulates in arriving at its decision? The answer no doubt must be that, even though in some cases it might not matter, in others it would, otherwise the lengthy debates about the meaning of these formulations and the circumstances in which they apply would be unnecessary.

A preliminary question, then, is whether this is one of those cases in which a difference in the standard of review would make a difference in the outcome. The ultimate issue is whether the Board correctly applied the Section 112 Para.1 enablement mandate and its implicit requirement of practical utility, or perhaps more accurately the underlying requirement of Section 101, to the facts of this case. As we have

explained, the issue breaks down into two subsidiary issues: (1) whether a person of ordinary skill in the art would conclude that the applicants had sufficiently described particular diseases addressed by the invention, and (2) whether the Patent Act supports a requirement that makes human testing a prerequisite to patentability under the circumstances of this case.

The first subsidiary issue, whether the application adequately described particular diseases, calls for a judgment about what the various representations and discussions contained in the patent application's specification would say to a person of ordinary skill in

the art. We have considered that question carefully, and, for the reasons we explained above in some detail, we conclude that the Board's judgment on this question was erroneous. Our conclusion rests on our understanding of what a person skilled in the art would gather from the various art cited, and from the statements in the application itself. We consider the Board's error to be sufficiently clear that it is reversible whether viewed as clear error or as resulting in an arbitrary and capricious decision.

The second subsidiary issue, whether human testing is a prerequisite to patentability, is a pure question of law: what does the practical utility requirement mean in a case of this kind. Under either our traditional standard or under the APA standard no deference is owed the Agency on a question of law, and none was accorded.

If the question concerning the standard of review, raised by the Commissioner, is to be addressed meaningfully, it must arise in a case in which the decision will turn on that question, and, recognizing this, the parties fully brief the issue. This is not that case. We conclude that it is not necessary to the disposition of this case to address the question raised by the Commissioner; accordingly, we decline the invitation to do so.

III. CONCLUSION

The Board erred in affirming the examiner's rejection under 35 U.S.C. Section 112 Para.1. The decision is *reversed*. *REVERSED* .

- End of Case -

UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE BOARD OF PATENT APPEALS AND INTERFERENCES

Ex parte JEFFERSON J. GREGORY,
ROBERT G. BRUNS, DEAN R. CIROTTA,
THOMAS K. ROGERS III, and CHARLES L. PAMPLIN III

Appeal 2008-005266
Application 10/360,208
Technology Center 1600

Decided:[1] June 22, 2009

Before DONALD E. ADAMS, DEMETRA J. MILLS, and
LORA M. GREEN, *Administrative Patent Judges*.

GREEN, *Administrative Patent Judge*.

DECISION ON APPEAL

This is a decision on appeal under 35 U.S.C. § 134 from the Examiner's final rejection of claims 1, 8-10, 16-18, and 21. We have jurisdiction under 35 U.S.C. § 6(b).

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[1] The two-month time period for filing an appeal or commencing a civil action, as recited in 37 C.F.R. § 1.304, begins to run from the decided date shown on this page of the decision. The time period does not run from the Mail Date (paper delivery) or Notification Date (electronic delivery).

STATEMENT OF THE CASE

The claims are directed to an oral trimethobenzamide formulation that may be used to treat and control nausea and/or vomiting. Claim 1 is representative of the claims on appeal, and reads as follows:

1. An oral trimethobenzamide composition for treating and controlling nausea and/or vomiting comprising 300mg trimethobenzamide hydrochloride and a suitable pharmaceutical excipient, wherein said oral trimethylbenzamide composition is at least about as effective as a 200mg intramuscular (I.M.) trimethobenzamide HCL injectable formulation in treating and controlling nausea and/or vomiting.

The Examiner relies on the following references:

Howard C. Ansel et al., "*Pharmaceutical Dosage Forms and Drug Delivery Systems*", 7th ed. 125, (1999).

Trimethobenzamide Hydrochloride Injection and Capsules, Federal Register Notice, 44(6): 2017 (1979).

We affirm.

ISSUES

The Examiner concludes that claims 1, 8-10, 16-18, and 21 would have been obvious over the combination of the FDA Federal Register notice issued in 1979 and Ansel.

Appellants contend that the ordinary artisan reading the FDA directive would have reformulated their 100 mg and 250 mg capsules to 200 mg and 400 mg, respectively, and thus the FDA directive teaches away from a 300

mg oral formulation. Appellants contend further that the patentability of claim 1 is supported by objective evidence of non-obviousness.

Thus, the issues on appeal are:

Have Appellants demonstrated that the Examiner erred in concluding that the claims on appeal are rendered obvious by the combination of the FDA Federal register notice issued in 1979 and Ansel;

And have Appellants demonstrated that, even if a prima facie case has been established, that the Examiner erred in not considering objective evidence of non-obviousness?

FINDINGS OF FACT

FF1 "Trimethobenzamide hydrochloride is a prescription drug that has been available in the market since the 1960s." (Spec. 2.) "Even though trimethobenzamide hydrochloride has been widely available for many years, the only routes and dosage forms that have been approved by the FDA are: 100 mg and 250 mg capsules; 100 mg and 200 mg suppositories; and 100 mg/ml in 2-ml ampules and prefilled syringes and in 20-ml vials as injectables. The injectable form is intended for intramuscular administration only; it is not recommended for intravenous use." (*Id.* at 3.)

FF2 In 1979, the FDA published a notice stating that trimethobenzamide capsules containing 100 mg or 250 mg of the drug were "not approximately bioequivalent to a 200-milligram intramuscular dose and do not achieve levels necessary to effectively treat or control nausea and vomiting." (*Id.* at 5.) Thus, the FDA stated that 100 mg and 250 mg capsules must be reformulated into 200 mg and 400 mg capsules "to achieve approximate

bioequivalence to a 200-milligram intramuscular dose." (*Id.*) The Specification discloses that "[n]otwithstanding this FDA notice, which was published more than 23 years ago, there is no oral trimethobenzamide dose available today which is approximately bioequivalent to a 200-milligram intramuscular dose or which achieves plasma levels effective to control nausea and vomiting." (*Id.*)

FF3 According to the Specification, "[q]uite amazingly, it has been discovered that an oral dose of about 300 mg of trimethobenzamide is uniquely approximately bioequivalent to a 200 mg intramuscular (I.M.) trimethobenzamide HCl injectable formulation, whereas an oral dose of about 400 milligrams of trimethobenzamide is not." (*Id.* at 6.)

FF4 The Specification teaches further that "it has been discovered, quite unexpectedly, that the bioequivalency (PK) parameters of an oral dose of about 400 mg of trimethobenzamide are uniquely approximately at least about 20% greater than the corresponding bioequivalency (PK) parameters for a 200 mg intramuscular (I.M.) trimethobenzamide HCl injectable formulation." (*Id.* at 6-7.)

FF5 The Examiner rejects claims 1, 8-10, 16-18, and 21 under 35 U.S.C. § 103(a) as being obvious over the combination of FDA Federal register notice issued in 1979 (Applicants' admission in the Specification) and Ansel (Ans. 3). As Appellants do not argue the claims separately, we focus our analysis on claim 1, and claims 8-10, 16-18, and 21 stand or fall with that claim. 37 C.F.R. § 41.37(c)(1)(vii).

FF6 According to the Examiner:

> Applicants admit on pages 5-6 of the instant specification that a FDA advised public that trimethobenzamide capsules

> comprising 100 mg and 250 mg drug should be reformulated to 200 and 400 mg respectively because the bioavailability of the 100 and 250 mg dosages are not approximately equivalent to the 200 mg IM injection formulations containing the drug. Thus, by applicants' own admission the need to improve the oral dosage formulations of trimethobenzamide has been recognized.

(Ans. 3.)

FF7 The notice issued by the FDA "reclassifies trimethobenzamide and hydrochloride injection and capsules to effective for certain indications and to lacking substantial evidence of effectiveness for their other less-than-effective indications," and "states that to obtain effective plasma levels for these drug products, a dosage of 200 milligrams intramuscularly or 400 milligrams orally is required, and that as part of the marketing conditions for the capsule dosage form, the capsules, now containing 100 milligrams or 250 milligrams must be reformulated to 200 milligrams or 400 milligrams respectively." 44 Fed. Reg. 2017 (1979).

FF8 The notice further states that:

> The relative bioavailability or extent of absorption of the capsule in the two studies was 50-62 percent of that of the intramuscular injection. As the oral route of administration produced blood levels which were approximately half of the levels produced by the intramuscular route, the oral route should be approximately two times the intramuscular dose.

Id. at 2019.

FF9 Thus, the following statement was added to the Action section:

> ORAL AND PARENTAL TRIMETHOBENZAMIDE ARE NOT BIOEQUIVALENT, AN ORAL DOSE OF 400 MILLIGRAMS OF TRIMETHOBENZAMIDE YIELDS

> PLASMA LEVELS APPROXIMATELY EQUAL TO A 200-MILLIGRAM INTRAMUSCULAR DOSE. The systemic bioavailability of orally administered trimethobenzamide is about 60 percent of the bioavailability of intramuscularly administered drug, possibly because of slow absorption and rapid liver metabolism (first pass effect). This difference is manifested as diminished peak blood levels and a diminished area under the plasma concentration curve following oral, as compared to parenteral administration.

Id.

FF10 Ansel is cited by the Examiner for its discussion of various routes of drug administration, and that "drugs administered orally are destroyed or inactivated in the GI tract or are poorly absorbed to provide a satisfactory response and that the parental administration requires smaller doses of drugs." (Ans. 3.)

FF11 The Examiner concludes:

> Thus, it is evident from the teachings of Ansel as well as the FDA notice that the injection formulations require smaller doses than oral route of administration. Therefore, it would have been obvious for one of an ordinary skill in the art at the time of the instant invention was made to optimize the amounts of trimethobenzamide in an oral formulations, based on the suggestion of FDA that the 100 and 250 mg doses to be increased to 200 and 400 mg respectively because it is well established (from the teachings of Ansel) that the parenteral formulations require smaller doses than the corresponding oral formulations and that in order to achieve the same bioavailability (with oral and parenteral), one requires higher dosages of drug in an oral formulation. Accordingly, one of an ordinary skill in the art would have been motivated to optimize the amounts of oral trimethobenzamide (higher than 250) with an expectation to achieve the optimum bioavailability desired.

(*Id.* at 3-4.)

FF12 Appellants have not supplemented the record with any evidence of non-obviousness beyond what is in the FDA notice.

PRINCIPLES OF LAW

The question of obviousness is resolved on the basis of underlying factual determinations including: (1) the scope and content of the prior art; (2) the level of ordinary skill in the art; (3) the differences between the claimed invention and the prior art; and (4) secondary considerations of nonobviousness, if any. *Graham v. John Deere Co.*, 383 U.S. 1, 17 (1966).

In *KSR Int'l v. Teleflex Inc.*, 550 U.S. 398, 415 (2007), the Supreme Court rejected a rigid application of a teaching-suggestion-motivation test in the obviousness determination. The Court emphasized that "the [obviousness] analysis need not seek out precise teachings directed to the specific subject matter of the challenged claim, for a court can take account of the inferences and creative steps that a person of ordinary skill in the art would employ." *Id.* at 418. Thus, an "[e]xpress suggestion to substitute one equivalent for another need not be present to render such substitution obvious." *In re Fout*, 675 F.2d 297, 301 (CCPA 1982).

Further,

> [i]f a person of ordinary skill can implement a predictable variation, § 103 likely bars its patentability. For the same reason, if a technique has been used to improve one device, and a person of ordinary skill in the art would recognize that it would improve similar devices in the same way, using the technique is obvious unless its actual application is beyond his or her skill.

KSR., 550 U.S. at 418. It is proper to "take account of the inferences and creative steps that a person of ordinary skill in the art would employ." *Id.* *See also id.* at 421 ("A person of ordinary skill is also a person of ordinary creativity, not an automaton.").

"In cases involving ranges . . . even a slight overlap in range establishes a *prima facie* case of obviousness." *In re Peterson*, 315 F.3d 1325, 1329 (Fed. Cir. 2003). In addition, as noted by the *Peterson*, "[t]he normal desire of scientists or artisans to improve upon what is already generally known provides the motivation to determine where in a disclosed set of percentage ranges is the optimum combination of percentages." *Id.* 1330.

The prima facie case of obviousness can be rebutted "by establishing 'that the [claimed] range is critical, generally by showing that the claimed range achieves unexpected results relative to the prior art range.'" *Id.* (alteration in original). Such a showing must be commensurate in scope with the claims. *Id.* In addition, mere improvement in properties is not always sufficient to demonstrate unexpected results. *In re Soni*, 54 F.3d 746, 751 (Fed. Cir. 1995).

The other way in which the prima facie case may be rebutted is by demonstrating that the "prior art teaches away from the claimed invention in any material respect." *Peterson*, 315 F.3d at 331. *See also In re Geisler*, 116 F.3d 1465, 1469 (Fed, Cir. 1997) (citing *in re Malagari*, 499 F.2d 1297, 1303 (CCPA 1974)).

Moreover, "[w]hen prima facie obviousness is established and evidence is submitted in rebuttal, the decision-maker must start over." *In re*

Rinehart, 531 F.2d 1048, 1052 (CCPA 1976); *In re Hedges*, 783 F.2d 1038, 1039 (Fed. Cir. 1986) ("If a prima facie case is made in the first instance, and if the applicant comes forward with reasonable rebuttal, whether buttressed by experiment, prior art references, or argument, the entire merits of the matter are to be reweighed"). Thus, all of the evidence must be considered under the *Graham* factors in reaching the obviousness determination.

In speaking about the relationship of patent law and FDA law, the Federal Circuit has noted:

> On the basis of animal studies, and controlled testing in a limited number of humans (referred to as Phase I testing), the Food and Drug Administration may authorize Phase II clinical studies. See 21 U.S.C. § 355(i)(1); 5 C.F.R. § 312.23 (a)(5), (a)(8) (1994). Authorization for a Phase II study means that the drug may be administered to a larger number of humans, but still under strictly supervised conditions. The purpose of a Phase II study is to determine primarily the safety of the drug when administered to a larger human population, as well as its potential efficacy under different dosage regimens. See 21 C.F.R. § 312.21(b). FDA approval, however, is not a prerequisite for finding a compound useful within the meaning of the patent laws. . . . . Usefulness in patent law, and in particular the context of pharmaceutical inventions, necessarily includes the expectation of further research and development. The stage at which an invention in this field becomes useful is well before it is ready to be administered to humans. Were we to require Phase II testing in order to prove utility, the associated costs would prevent many companies from obtaining patent protection on promising new inventions, thereby eliminating an incentive to pursue, through research and development, potential cures in many crucial areas such as the treatment of cancer.

In re Brana, 51 F.3d. 1560, 1568 (Fed. Cir. 1995) (citations omitted). Although the above statements were made in the context of utility and enablement, the clear inference is that FDA determinations are not controlling on patentability, which would include the obviousness determination.

ANALYSIS

Appellants argue that the "FDA recognized a need for an oral formulation of trimethobenzamide hydrochloride that would yield plasma levels approximately equivalent to a 200 mg IM injection," and the FDA required that existing oral capsules be reformulated into either 200 mg or 400 mg capsules, and that the 400 mg capsule would be equivalent to the 200 mg IM injection (App. Br. 6). Thus, Appellants assert, the ordinary artisan reading the FDA directive would have reformulated their 100 mg and 250 mg capsules to 200 mg and 400 mg, respectively, not 300 mg as claimed (*id.*). Ansel, Appellants assert, is unrelated to the claims on appeal, as it "merely makes a general statement that one may employ smaller dosages of a drug when administered parentally as opposed to orally." (*Id.*)

Appellants argue further, "the prior art taught only the use of a 400 mg oral formulation to be equivalent to the 200 mg IM injection." (*Id.* at 7.) Appellants argue further that the "prior art does not suggest a range for oral administration," and "does not suggest a formula for one to determine an equivalent oral dosage strength from an IM injection strength." (*Id.*) According to Appellants, "[w]ithout any direction in the prior art, it would

not be obvious to one skilled in the art how to determine what oral dosage strength of a particular drug would be equivalent to an injectable." (*Id.* at 8.)

Appellants note that the Examiner concludes "that ' . . . a skilled artisan would have readily calculated the equivalent dosages of oral trimethobenzamide to that of intramusculsar injection . . .,'" which Appellants contend "is absurd." (*Id.* at 9.) Appellants assert that:

> The Examiner fails to note that someone in the art did calculate what it believed to be the oral dose of trimethobenzamide that would be equivalent to the 200 mg IM dose. It was calculated by the U.S. Food and Drug Administration and it was wrong.

(*Id.*)

Appellants argue further that there is objective evidence of non-obviousness (App. Br. 8). According to Appellants:

> In this case the prior art showed there was an unmet medical need for an oral dosage strength of trimethobenzamide hydrochloride that would be equivalent to a 200 mg IM injection. The prior art taught that the oral dosage would be 400 mg.
>
> Applicants were the first to show that it is a 300 mg oral dosage that provides optimal control of nausea and vomiting. The success of Applicants invention is evidenced by the FDA approval of its 300 mg product and the commercial acceptance of the invention.

(App. Br. 8.)

Appellants' arguments have been carefully considered, but are not convincing. First, as to Appellants' argument that the prior art does not teach a range, Appellants acknowledge that oral formulation comprising 100 mg, 200 mg, 250 mg, and 400 mg have been approved by the FDA in the

past. Thus, we agree with the Examiner that a range of trimethobenzamide is known to be useful for the treatment of nausea, wherein the range extends from 100 mg to 400 mg. Although that range is not explicitly taught by the FDA notice, one of ordinary skill in the pharmaceutical arts would recognize it as such. The ordinary artisan in the pharmaceutical art, which is a heavily regulated industry, would understand that only certain dosage amounts in a range that would have been obvious under the patent laws would eventually be approved for clinical use by the FDA. The ordinary artisan understands that the showing required to demonstrate that a compound intended for clinical use is patentable under the patent statute is not as strict as the showing required by the FDA for approval for *in vivo* clinical use. *See, e.g.*, *Brana*, 51 F.3d. at 1568 ("FDA approval, however, is not a prerequisite for finding a compound useful within the meaning of the patent laws.").

As we agree with the Examiner that the art establishes a range, and as claim 1 is drawn to an amount in that range, the subject matter of claim 1 is prima facie obvious under *Peterson*. We thus determine if Appellants have rebutted that prima facie case by determining if Appellants have established that the prior art teaches away from the claimed amount in any material respect, or have established that the claimed amount is critical.

As noted by Appellants, the FDA in 1979, 24 years before Appellants' filing date, reclassified trimethobenzamide capsules, and stated that "to obtain effective plasma levels for these drug products, a dosage of 200 milligrams intramuscularly or 400 milligrams orally is required, and that as part of the marketing conditions for the capsule dosage form, the capsules,

now containing 100 milligrams or 250 milligrams must be reformulated to 200 milligrams or 400 milligrams respectively." (FF7.)

The notice stated, however, that the "relative bioavailability or extent of absorption of the capsule in the two studies was 50-62 percent of that of the intramuscular injection," and thus the FDA acknowledged that there was some variability in the data (FF8). Moreover, while noting that an oral dose of 400 mg yields plasma levels *approximately* equal to that of a 200 mg intramuscular dose, as noted by the Examiner (Ans. 6), the FDA also stated that the "systemic bioavailability of orally administered trimethobenzamide is about 60 percent of the bioavailability of intramuscularly administered drug." (FF9.) Thus, 60% of a 400 mg dose would be approximately equivalent to a 240 mg IM dose, and 60% of the claimed 300 mg dose would be approximately equivalent to a 180 mg IM dose, which is "about as effective" as a 200 mg IM dose.

Thus, given the variability reported by the FDA, that is, the fact that the FDA notice stated that the "relative bioavailability or extent of absorption of the capsule in the two studies was 50-62 percent of that of the intramuscular injection," and given that the FDA notice states that the systemic bioavailability of orally administered trimethobenzamide is *about* 60 percent of the bioavailability of intramuscularly administered drug, the ordinary artisan would have been motivated to reconsider the pharmacodynamics of trimethobenzamide in order to find other dosage amounts that may be at least about as effective as a 200mg intramuscular (I.M.) trimethobenzamide. That finding is further supported by the fact that 24 years had passed since the FDA directive, and given that the background

knowledge in the art and the technology available in the pharmaceutical industry had substantially increased in those 24 years, the ordinary artisan would have been further motivated to take another look at the pharmacodynamics of trimethobenzamide, a drug that has already been approved by the FDA for clinical use. As it is the "normal desire of scientists or artisans to improve upon what is already generally known provides the motivation to determine where in a disclosed set of percentage ranges is the optimum combination of percentages," *Peterson*, we conclude that the prior art does not teach away from the composition of claim 1 in a material way. *See In re Aller*, 220 F.2d 454, (CCPA 1955) (noting that "where the general conditions of a claim are disclosed in the prior art, it is not inventive to discover the optimum or workable ranges by routine experimentation); *see also KSR*, 550 U.S. at 421 ("When there is a design need or market pressure to solve a problem and there are a finite number of identified, predictable solutions, a person of ordinary skill has good reason to pursue the known options within his or her technical grasp. If this leads to the anticipated technical success, it is likely the product not of innovation but of ordinary skill and common sense.").

We also conclude that Appellants have not established that the claimed amount is critical. As noted above, the FDA noted there was variability in the data, and also noted that the systemic bioavailability of orally administered trimethobenzamide is about 60 percent of the bioavailability of intramuscularly administered drug. As 60% of a 300 mg oral dose would be *approximately* equivalent to a 180 mg IM dose, we conclude that the ordinary artisan would not find it unexpected that a 300 mg

oral dose would be "a least about as effective" as a 200 mg IM dose as is required by Appellants' claim 1.

While Appellants assert that the criticality of the amount is established by the FDA approval of its 300 mg product, FDA determinations are not controlling on patentability determinations, which would include the obviousness determination. In addition, while Appellants assert that there is commercial acceptance of the invention, Appellants have provided no evidence on the record that would support commercial success, or even commercial acceptance.

CONCLUSION(S) OF LAW

We conclude that:

Appellants have not demonstrated that the Examiner erred in concluding that the claims on appeal are rendered obvious by the combination of the FDA Federal register notice issued in 1979 and Ansel; and

Appellants have not demonstrated that, even if a prima facie case has been established, the Examiner erred in not considering objective evidence of non-obviousness.

We thus affirm the rejection of claims 1, 8-10, 16-18, and 21 under 35 U.S.C. § 103(a) as being obvious over the combination of FDA Federal Register Notice and Ansel.

TIME PERIOD FOR RESPONSE

No time period for taking any subsequent action in connection with this appeal may be extended under 37 C.F.R. § 1.136(a).

AFFIRMED

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Source: USPQ, 2d Series (1986 - Present) > U.S. Court of Appeals, Federal Circuit > In re Chupp, 2 USPQ2d 1437 (Fed. Cir. 1987)

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2 USPQ2d 1437
In re Chupp
U.S. Court of Appeals Federal Circuit
No.86-1631
Decided April 15, 1987
816 F2d 643

Headnotes

PATENTS

[1] Patentability/Validity -- Obviousness -- Evidence of (▶ 115.0903)

Patent and Trademark Office Board of Patent Appeals and Interferences improperly rejected claimed herbicidal compound for obviousness under 35 USC 103, since there is no set number of crops on which compound's superiority must be shown, and since compound's superior activity on quackgrass and yellow nutsedge in corn and soybeans is sufficient to rebut prima facie case of obviousness.

Case History and Disposition

Appeal from the Patent and Trademark Office, Board of Patent Appeals and Interferences.

Application for patent, Serial No. 358,967, by John P. Chupp. From decision affirming examiner's final rejection of claims 1 and 12, applicant appeals. Reversed.

Attorneys

Dale H. Hoscheit, and Banner, Birch, McKie & Beckett, both of Washington, D.C. (William I. Andress, St. Louis, Mo., on the brief) for appellant.

Richard E. Schafer, associate solicitor, Office of the Solicitor (Joseph F. Nakamura, solicitor, and Fred E. McKelvey, deputy solicitor, on the brief) for Patent and Trademark Office.

Judge

Before Markey, Chief Judge, Friedman, Circuit Judge, and Re, Chief Judge (U.S. Court of International Trade, sitting by designation).

Opinion Text

Opinion By:

Markey, Chief Judge.

Appeal from a decision of the United States Patent and Trademark Office (PTO) Board of Patent Appeals and Interferences (board), affirming the examiner's final rejection of claims 1 and 12 in application Serial No. 358,967 under 35 U.S.C. § 103. We reverse.

BACKGROUND

On March 17, 1982, John P. Chupp (Chupp) filed a continuation-in-part application, assigned to Monsanto Company, entitled "Herbicidal 2-Haloacetanilides." The application contained 41 claims to a variety of chemical compounds within the generic class of 2-haloacetanilides, a method for using the compounds to combat weeds in crops, and an herbicidal composition containing a 2-haloacetanilide.

The examiner rejected all claims under 35 U.S.C. § § 102(a) and 103, stating that the references, including Swiss patents 579,348 (issued July 31, 1976) and 585,191 (issued January 15, 1977) (Swiss patents), rendered the claimed compounds, methods and compositions *prima facie* obvious.

Chupp canceled all but eleven claims and limited the remaining claims to a single compound, N-(ethoxy *methyl*)-2'-trifluoromethyl-6'-methyl-2-chloroacetanilide. That compound differs by a single methylene group (-CH_2-) from the closest prior art compound, N-(ethoxy *ethyl*)-2'-trifluoromethyl-6'-methyl-2-chloroacetanilide, disclosed in the Swiss patents. Chupp apparently did not challenge the examiner's conclusion that the Swiss patents rendered the claimed compound *prima facie* obvious.

To rebut the *prima facie* case of obviousness, Chupp submitted a declaration discussing the results of tests comparing the herbicidal activity of the claimed compound with that of the closest prior art compounds and with two commercial herbicides. The tests compared the compounds' ability to control two weeds, quackgrass and yellow nutsedge, in two crops, corn and soybeans. it is undisputed that the claimed compound gave superior results, exhibiting selectivity factors (crop safety combined with weed-killing activity) at least five times greater than those of the closest prior art compounds. The declarant concluded "the herbicidal properties of the compound of the invention herein are unquestionably outstandingly superior to those of the relevant prior art; the unexpected and unpredictable magnitude of superiority is evidenced by the many-fold increase in unit activity against weeds and high crop safety."

The examiner finally rejected all claims under 35 U.S.C. § 103 as being unpatentable over the Swiss patents, saying that comparative testing using only two weeds and two crops was insufficient to establish unexpected herbicidal activity.

Chupp submitted two more declarations. The first presented data from a second comparative test of the claimed compound and the closest prior art compounds, again comparing their ability to control quackgrass and yellow nutsedge in corn and soybeans. The second declaration, from Dr. F. W. Slife, a University of Illinois agronomy professor, analyzed the results of both comparative tests and praised "the superior performance of the invention compound vis-a-vis the prior art compounds as completely unexpected considering the close chemical structure of the test compounds."

The examiner allowed claims 36 and 37 for a method of combatting weeds in corn and soybeans using the claimed compound, but continued to reject the remaining claims. The examiner said that more extensive comparative testing was needed because the data disclosed in the specification showed the claimed compound would not be superior to prior art compounds for crops other than corn and soybeans.

Chupp appealed the rejection to the board, canceling all remaining rejected claims except 1 and 12. Claim 1 sets forth the compound and its structure. Claim 12 sets forth an "[h]erbicidal composition comprising an adjuvant and a herbicidally effective amount of the compound" and the compound's structure.

The board *affirmed* the rejection of claims 1 and 12, holding that Chupp's evidence was

insufficient to rebut the *prima facie* case of obviousness. The board said the claimed compound had no new selective herbicides, so it was no surprise that the claimed compound was also a selective herbicide. *Prior art herbicides were useful in many crops; the specification data showed that the claimed compound was at best a run-of-the-mill performer in crops other than corn and soybeans. The board held that

because the claims were limited to no particular weed or crop, "the showing is not fairly representative of that which is encompassed by the claims." Therefore, concluded the board, the evidence of superiority in corn and soybeans could not rebut the *prima facie* obviousness of the "invention as a whole".

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* An herbicide is "selective" if it controls weeds without injuring the crop.

The board further stated that Swiss patent 579,348 taught that N-alkoxy *methyl* chloroacetanilides (like the claimed compound) were superior in activity to the corresponding N-alkoxy *ethyl* chloroacetanilides (like the closest prior art compound). Thus, said the board, "the results shown by appellant in his declaration are only those which would have been expected."

ISSUE

Whether the board erred in sustaining the rejection of claims 1 and 12.

It is undisputed that the claimed compound is novel. That its superior activity in corn and soybeans is a new and unexpected property is confirmed by the allowance of the method claims to its use on corn and soybeans. *See In re McLamore* , 379 F.2d 985, 988-90, 154 USPQ 114, 117-18 (CCPA 1967) (the grant of method claims persuasive of compound's nonobviousness).

Chupp argues that this case is controlled by *In re Papesch* , 315 F.2d 381, 137 USPQ 43 (CCPA 1963), and the line of cases following it. In *Papesch* , one of our predecessor courts *reversed* a rejection of claims to compounds structurally similar to a prior art compound, but which unexpectedly possessed antiinflammatory properties. The *Papesch* court held, "From the standpoint of patent law, a compound and all of its properties are inseparable; they are one and the same thing." 315 F.2d at 391, 137 USPQ at 51. Under the *Papesch* doctrine, evidence of unobvious or unexpected advantageous properties may rebut a *prima facie* case of obviousness based on structural similarities. *Id* . at 386-87, 137 USPQ at 48. Such evidence may include data showing that a compound is unexpectedly superior in a property it shares with prior art compounds. *E.g., In re Lunsford* , 357 F.2d 380, 148 USPQ 716 (CCPA 1966). Chupp says the undisputed evidence that the claimed compound possesses superior herbicidal activity on quackgrass and yellow nutsedge in corn and soybeans shows that the compound possesses unobvious and unexpected advantageous properties rebutting the *prima facie* case of obviousness.

The Solicitor counters that, under 35 U.S.C. § 103, a compound is patentable only if its "subject matter as a whole" would not have been obvious at the time the compound was made. The Solicitor, like the board, maintains that *Papesch* does not help Chupp because the claimed compound possesses no new or unexpected property; it possesses the same property as the prior art compounds, i.e., selective herbicidal activity. The Solicitor dismisses the claimed compound's superiority in respect of corn and soybeans, saying its herbicidal utility in other crops, which the Solicitor argues represents its properties "as a whole", is only so-so.

We do not agree with the Solicitor's construction of *Papesch*. *Papesch* held that a compound can be patented on the basis of its properties; it did not hold that those properties must produce superior results in every environment in which the compound may be used. To be patentable, a compound need not excel over prior art compounds in all common properties. See *United States* v. *Ciba-Geigy Corp* ., 508 F.Supp. 1157, 1169, 211 USPQ 529, 535-36 (D.N.J. 1979). Evidence that a compound is unexpectedly superior in one of a spectrum of common properties, as here, can be enough to rebut a *prima facie* case of obviousness. *In re Ackermann* , 444 F.2d 1172, 1176, 170 USPQ 340, 343 (CCPA 1971).

The Solicitor urges that *In re Payne* , 606 F.2d 303, 203 USPQ 245 (CCPA 1979), directs a contrary holding. We disagree. In *Payne* , the Court of Customs and Patent Appeals said the mere submission of

some evidence that a new compound possesses some unpredictable properties does not require an automatic conclusion of nonobviousness in every case. 606 F.2d at 316, 203 USPQ at 256-57; *see also In re de Montmollin* , 344 F.2d 976, 979, 145 USPQ 416, 417 (CCPA 1965). The *Payne* court held that the evidence submitted in that case was *insufficient* to rebut a *prima facie* case of obviousness, because the claimed compound

Page 1440

was compared with too few prior art compounds. 606 F.2d at 316, 203 USPQ at 256-57. That is not the situation in this case.

In *Ackermann* , the Court of Customs and Patent Appeals rejected an argument similar to the one the PTO advances here. Ackermann sought to patent an optical brightener compound. To rebut a *prima facie* case of obviousness, Ackermann submitted evidence that the claimed compound was ten times more effective on polyester fibers than were the closest prior art compounds. The specification stated, however, that the claimed compound could be used as an optical brightener on a variety of materials. In affirming the examiner's rejection, the board said that the evidence of superiority on polyester fibers did not support the breadth of the claim, which covered the compound for all brightening purposes. The Court of Customs and Patent Appeals *reversed*, holding that the evidence of superiority on polyester fibers "pertain[ed] to the full extent of subject matter being claimed" (i.e., the compound per se), and was enough to show that the compound possessed an unexpected difference in properties over the prior art. 444 F.2d at 1176, 170 USPQ at 343. That reasoning is fully applicable to this case.

The Solicitor contends, as above indicated, that the evidence demonstrating the claimed compound's superior performance in corn and soybeans does not show an *unexpected* difference in properties because the Swiss patents teach that similar compounds would be selective herbicides, and the comparative tests therefore show only what would reasonably have been predicted. The properties of a compound, however, may include an unexpectedly superior performance of the selective herbicidal activity. *E.g* ., *Lunsford* , 357 F.2d at 384, 148 USPQ at 720.

The evidence of record does not support the Solicitor's assertion that the claimed compound's properties are what would have been expected. The Swiss patents teach that their N-alkoxy *ethyl* compounds are superior to N-alkoxy *methyl* chloroacetanilides, contrary to the view of agronomists. Dr. Slife's declaration forcefully states, "I find no evidence in the cited Swiss patents which would lead me to expect that a novel compound such as that claimed herein [an N-alkoxymethyl chloroacetanilide] would have the superior properties it has exhibited." *See In re Blondel* , 499 F.2d 1311, 182 USPQ 294 (CCPA 1974) (reversing rejection of claims to compounds which prior art suggested would have longer-lasting pharmacological activity, where actual increase was beyond reasonable expectations).

The rejection here, though couched in § 103 language, resolves itself into one based on "undue breadth," the PTO's concern being that a claim to the compound would forestall its use by others on crops other than corn and soybeans, even though such use would produce no more satisfactory, or even less satisfactory, results. The PTO's concern is misplaced. There is no set number of crops on which superiority must be shown, and the expectation that persons would want to use the compound to produce inferior results (or would want to fight lawsuits over such uses) is false. One of this court's predecessors pointed out the impropriety of "undue breadth" rejections long ago. *E.g* ., *Ackermann* , 444 F.2d at 1176, 170 USPQ at 343; *In re Ruschig* , 343 F.2d 965, 978-79, 145 USPQ 274, 285-86 (CCPA 1965).

CONCLUSION

[1] Chupp's evidence that the claimed compound possesses superior herbicidal activity on quackgrass and yellow nutsedge in corn and soybeans is sufficient to rebut the *prima facie* case of obviousness. We conclude that the claimed subject matter would not have been obvious to one of ordinary skill in the art at the time the invention was made. The decision of the board affirming the rejection of claims 1 and 12 under 35 U.S.C. § 103 is *reversed*.

REVERSED

- End of Case -

UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE BOARD OF PATENT APPEALS AND INTERFERENCES

Ex parte
HANS-MICHAEL EGGENWEILER, ROCHUS JONAS, MICHAEL WOLF, MICHAEL GASSEN, and OLIVER POSCHKE

Appeal 2007-2495
Application 10/750,878
Technology Center 1600

Decided: November 27, 2007

Before TONI R. SCHEINER, ERIC GRIMES, and NANCY J. LINCK, *Administrative Patent Judges*.

Opinion for the Board filed by *Administrative Patent Judge* TONI R. SCHEINER.

Opinion Dissenting filed by *Administrative Patent Judge* NANCY J. LINCK.

SCHEINER, *Administrative Patent Judge.*

DECISION ON APPEAL

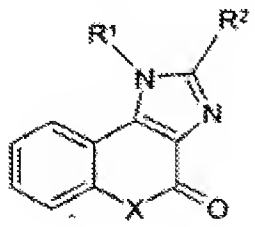
This is an appeal under 35 U.S.C. § 134 from the final rejection of claims 5-8.[1] The Examiner has rejected the claims as lacking enablement. We have jurisdiction under 35 U.S.C. § 6(b). We reverse.

DISCUSSION

The present invention is directed to a method of treating various conditions, including autoimmune diseases and tumors, by administering an imidazole derivative which, according to the Specification, "show[s] a specific inhibition of the 'Rolipram-insensitive' cAMP phosphodiesterase (PDE VII)" (Spec. 2: 14-16), and an "anti-inflammatory" "antagonistic effect on the production of TNFα (tumour necrosis factor)" (*id.* at 3: 8-9 and 16), and "may also inhibit the growth of tumour cells" (*id.* at 3: 30-31).

Claims 5-8 are on appeal. Independent claim 5 is representative:

> 5. A method of treating allergic disorders, asthma, chronic bronchitis, atopic dermatitis, psoriasis, inflammatory disorders, autoimmune diseases, osteoporosis, transplant rejection reactions, cachexia, tumor growth, tumor metastases, sepsis, or atherosclerosis comprising administering, to a host in need thereof, an effective amount of a compound of formula I



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> in which

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[1] Claim 9 is also pending, but has been withdrawn from consideration.

R^1 is H, A, benzyl, indan-5-yl, 1,2,3,4-tetrahydronaphthalen-5-yl, dibenzothien-2-yl, or phenyl which is unsubstituted or mono-, di- or trisubstituted by Hal, A, A-CO-NH, benzyloxy, alkoxy, COOH or COOA,
R^2 is H or A,
X is O or S,
Hal is F, Cl, Br or I,
A is alkyl with 1 to 6 C atoms,
or a physiologically acceptable salt or solvate thereof.

The Examiner rejected the claims under 35 U.S.C. § 112, first paragraph, as failing to comply with the enablement requirement, in three separate rejections, each of which covers claims 5-8. The first rejection concerns treatment of tumors, the second rejection concerns treatment of autoimmune disorders, and the third rejection concerns treatment of memory disturbances.

Treatment of Tumors

Claims 5-8 stand rejected under 35 U.S.C. § 112, first paragraph, as lacking enablement. According to the Examiner, the Specification "does not provide sufficient information that all tumors are treatable by the herein claimed compounds described in the methods claimed" (Answer 3).

It is well settled that "a specification disclosure which contains a teaching of the manner and process of making and using the invention in terms which correspond in scope to those used in describing and defining the subject matter sought to be patented *must* be taken as in compliance with the enabling requirement of the first paragraph of § 112 *unless* there is reason to doubt the objective truth of the statements contained therein which must be relied on for enabling support." *In re Marzocchi*, 439 F.2d 220, 223 (CCPA

1971) (emphasis in original). "[It] is incumbent upon the Patent Office, whenever a rejection on this basis is made, to explain why it doubts the truth or accuracy of any statement in a supporting disclosure and to back up assertions of its own with acceptable evidence or reasoning which is inconsistent with the contested statement." *Id.* at 224. In other words, "the PTO bears an initial burden of setting forth a reasonable explanation as to why it believes that the scope of protection provided by [the] claim[s] is not adequately enabled by the description of the invention provided in the specification of the application; this includes, of course, providing sufficient reasons for doubting any assertions in the specification as to the scope of enablement." *In re Wright*, 999 F.2d 1557, 1561 (Fed. Cir. 1993).

Thus, the issue raised by this appeal is *not* whether Appellants have established that the disclosure is enabling for the scope of the claims; the issue is whether the PTO has met its "initial burden of setting forth a reasonable explanation as to why" it is not.

Here, the Examiner's position is essentially that "[t]he nature of the invention is complex in that it encompasses the treatment of all types of tumors" (Answer 4), "there is no known anticancer agent which is effective against all cancers" (*id.* at 5), and practicing the invention would require "undue, unpredictable experimentation" "for each type of cancer" (*id.* at 7).

On this record, we find that the Examiner has not adequately explained why practicing the invention would have required undue experimentation. First, the Examiner's reasoning is extremely generalized, and does not begin to address Appellants' objective statements regarding the inhibitory effects of the subject imidazole derivatives on phosphodiesterase

(PDE) VII (Spec. 2: 11-16), their antagonistic effects on the production of TNFα (Spec. 3: 8-9), or the role of phosphodiesterases and/or TNFα in cancer.

Second, the fact that "there is no known anticancer agent . . . effective against all cancers" is irrelevant. It is true of all known anticancer agents, and neither adds to nor detracts from the enablement of the instant derivatives. Finally, we know of no authority, and the Examiner cites none, that would require Appellants' imidazole derivatives to be "effective against all cancers" in order to support a claim directed to cancer treatment generally. On the contrary, a claim may encompass inoperative embodiments and still meet the enablement requirement of 35 U.S.C. § 112, first paragraph. *See Atlas Powder Co. v. E.I. Du Pont De Nemours & Co.*, 750 F.2d 1569, 1576, 224 USPQ 409, 413 (Fed. Cir. 1984), *In re Angstadt*, 537 F.2d 498, 504, 190 USPQ 214, 218 (CCPA 1976), *In re Cook*, 439 F.2d 730, 732, 169 USPQ 298, 300 (CCPA 1971).

In our view, the reasons cited in support of the Examiner's rejection do not provide a reasonable basis to question the adequacy of the disclosure provided for the claimed invention, and the Examiner's initial burden has not been met. Accordingly, the rejection of claims 5-8 under 35 U.S.C. § 112, first paragraph, is reversed.

Treatment of Autoimmune Disorders

The Examiner also rejected claims 5-8 under 35 U.S.C. § 112, first paragraph, because the Specification "while being enabling for rheumatoid arthritis, multiple sclerosis, Crohn's disease, diabetes mellitus, and ulcerative colitis, does not reasonably provide enablement for other autoimmune disorders" (Answer 7).

In this case, the Examiner's position is essentially that "[t]he nature of the invention is complex in that it encompasses the treatment of all types of autoimmune disorders" (Answer 8), "it is known that some drugs are useful for treating multiple autoimmune diseases, [but] other drugs are not as versatile" (*id.* at 9), and practicing the invention would require "undue experimentation" "for each type of autoimmune disease" (*id.* at 10).

This rejection suffers from the same infirmities as the preceding rejection. Moreover, no explanation is given for distinguishing between "rheumatoid arthritis, multiple sclerosis, Crohn's disease, diabetes mellitus, and ulcerative colitis," which the Examiner finds *are* enabled, and "other autoimmune disorders," which are not. Again, we find the reasons cited in support of the Examiner's rejection do not provide a reasonable basis to question the adequacy of the disclosure provided for the claimed invention, and the Examiner's initial burden has not been met. Accordingly, this rejection of claims 5-8 under 35 U.S.C. § 112, first paragraph, is reversed as well.

Treatment of Memory Disturbances

Finally, claims 5-8 stand rejected under 35 U.S.C. § 112, first paragraph, for lack of enablement, because the Specification "does not provide sufficient information that memory disturbances are treatable by the herein claimed compounds described in the methods claimed" (Answer 11).

However, the claims are no longer directed to treatment of memory disturbances. See Appellants' Amendment filed October 14, 2005. The rejection is reversed.

SUMMARY

We reverse all three of the Examiner's rejections for lack of enablement under the first paragraph of 35 U.S.C. § 112.

REVERSED

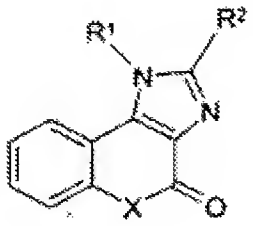
Dissenting Opinion by LINCK, *Administrative Patent Judge*

I respectfully dissent and would affirm the Examiner's § 112 ¶ 1 rejection of all the claims based on lack of enablement. Based on the record before us, particularly given the breadth of the claims and the Specification's limited disclosure, I do not believe Appellants' Specification would have enabled the full scope of their claims.

Claim 5, the only independent claim in the application, recites a method for treating a laundry list of largely unrelated ailments:

> allergic disorders, asthma, chronic bronchitis, atopic dermatitis, psoriasis, inflammatory disorders, autoimmune diseases, osteoporosis, transplant rejection reactions, cachexia, tumor growth, tumor metastases, sepsis, or atherosclerosis

with "an effective amount of a compound" from a genus of compounds:



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> in which R^1 is H, A, benzyl, indan-5-yl, 1,2,3,4-tetrahydronaphthalen-5-yl, dibenzothien-2-yl, or phenyl which is unsubstituted or mono-, di- or trisubstituted by Hal, A, A-CO-NH, benzyloxy, alkoxy, COOH or COOA, R^2 is H or A, X is O or S, Hal is F, Cl, Br or I, A is alkyl with 1 to 6 C atoms, or a physiologically acceptable salt or solvate thereof.

According to the Specification, these compounds are PDE VII inhibitors, although Appellants do not disclose the level of inhibition for a single compound within their genus (Spec. 2). Rather, the Specification merely discloses how a skilled artisan can determine whether they are inhibitors and, if so, how effective they are. (*See* Spec. 2 (the "affinity of the compounds for . . . (PDE VII) *is* determined by measuring their IC_{50} values" (emphasis added to show prophetic nature of teaching)).)

More significantly, in my view, Appellants provide very little, if any, evidence their many compounds would be useful in treating all or even a majority of cancers (or any other disease). According to Appellants, "PDE VII inhibitors *may* . . . inhibit the growth of tumour cells and are therefore suitable for tumour therapy." (Spec. 3.) Support for this suggestion is not based on Appellants' own work but rather on someone else's publication regarding a different inhibitor, i.e., PDE IV (Spec. 3). Appellants provide no examples, not even prophetic ones, to guide the skilled artisan how to use their claimed method to treat cancer (or any other disorder). Given Appellants' lack of meaningful teaching or direction, the Examiner reasonably doubted Appellants' assertions regarding effectively treating tumors and autoimmune diseases, without limitation (Answer *passim*) and appropriately refused to allow Appellants' application.

The law is well settled that enablement must be commensurate in scope with the claimed invention. *E.g., Liebel-Flarsheim Co. v. Medrad, Inc.*, 481 F.3d 1371, 1379 (Fed. Cir. 2007); *Genentech, Inc. v. Novo Nordisk*, 108 F.3d 1361, 1365 (Fed. Cir. 1997); *In re Wright*, 999 F.2d 1557, 1561 (Fed. Cir. 1993). A single embodiment *may* be sufficient, *if* that teaching

combined with the knowledge of the skilled artisan would enable the full scope of the claim. *See Johns Hopkins Univ. v. Cellpro Inc.*, 152 F.3d 1342, 1361 (Fed. Cir. 1998). However, in this case, in spite of the breadth of the claims and the well-recognized challenges in treating cancer and autoimmune diseases, *no* embodiment is disclosed.

While I agree with my colleagues that inoperative embodiments do not necessarily defeat patentability (*supra* p. 5 (citing, e.g., *Atlas Powder Co. v. E.I. du Pont De Nemours & Co.*, 750 F.2d 1569, 1576 (Fed. Cir. 1984)), "if the number of inoperative combinations becomes significant, and in effect forces one of ordinary skill in the art to experiment unduly in order to practice the claimed invention, the claims might indeed by invalid." *Id.* at 1576-77. That's the problem with this case. Appellants do not disclose a *single* embodiment showing that *any* of the compounds within their genus would be effective to treat *any* type of cancer (or *any* autoimmune disease), even *in vitro*.

The fact that "PDE inhibitors are well known to be implicated in signaling pathways which are instrumental in the formation of tumors" (Reply Br. 5), does not enable the treatment of tumors. Without more, the skilled artisan would not have had a reasonable expectation of success in doing so based on Appellants' very limited disclosure.

According to Appellants, "the question is . . . whether one of ordinary skill in [the] art could routinely make and test each compound, for a given utility, in order [to] ascertain whether a given compound is operative in the claimed method." (App. Br. 8.) The problem with Appellants' statement of the question is that it reflects what they've provided—an invitation to

experiment rather than an enabling disclosure. *See Brenner v. Manson*, 383 U.S. 519, 536 (1966) ("a patent is not a hunting license [or] a reward for the search, but compensation for its successful conclusion"), *quoted with approval in Genentech, Inc. v. Novo Nordisk*, 108 F.3d 1361, 1366 (Fed. Cir. 1997).

Under Appellants' test, if it were routine to test all their compounds in all their claimed treatments and none were found operative, the enablement requirement would still be satisfied. However, that is not the law: Their teachings must enable the full scope of their claims. Thus, although their genus of compounds and uses may include *some* inoperative embodiments, the number that are effective in treating cancer (or autoimmune disease) must bear a reasonable correlation to the scope of the claims. *In re Fisher*, 427 F.2d 833, 839 (CCPA 1970) ("scope of the claims must bear a reasonable correlation to the scope of enablement provided by the specification to persons of ordinary skill in the art"), *quoted with approval in Invitrogen Corp. v. Clontech Labs, Inc.*, 429 F.3d 1052, 1071 (Fed. Cir. 2005). "While every aspect of a generic claim certainly need not have been carried out by an inventor, or exemplified in the specification, reasonable detail must be provided in order to enable members of the public to understand and carry out the invention." *Genentech*, 108 F.3d at 1366.

I agree with the majority that the PTO bears the initial burden of "setting forth a reasonable explanation as to why it believes that the scope of protection provided" by the claims "is not adequately enabled by the description . . . provided in the specification" (*supra* p. 4) but do not agree the Examiner has failed to meet that burden, given the scope of Appellants' claims and their very limited description.

In my view, the Examiner has provided sufficient evidence and reasoned argument to prima facie support her lack of enablement rejection. The Examiner went through each of the *Wands* factors, finding the "nature of the invention is complex . . . exacerbated by the breadth of the claims;" the "guidance given by the specification . . . is limited," disclosing only that "'PDE VII inhibitors *may* also inhibit the growth of tumor cells;'" there is no working examples; "there is no known anticancer agent which is effective against all cancers" (citing Carter et al., Chemotherapy of Cancer (2nd ed. 1981)); "the existence of . . . a 'silver bullet' is contrary to our present understanding in oncology" because "cancers arise from a wide variety of sources;" "it is beyond the skill of oncologists today to get an agent to be effective against cancers generally;" "[c]ancers are especially unpredictable due to their complex nature;" and "it would require undue, unpredictable experimentation to practice the claimed invention . . . ." (Answer 3-7.) These findings are consistent with what the skilled artisan in the pharmaceutical field would have known at the time this application was filed (or even today).

Given the Examiner's reasonable explanation why she doubted Appellants' claims were enabled, it was up to Appellants to rebut her evidence. Given the record before us, I find they did not do so convincingly. While they argue the Carter reference "appear[s] to suggest that some drugs do not 'interact' with tumors located in the various areas listed" but does not explain "this 'interaction' and whether its significance translates to therapeutic modalities" (Reply Br. 6). In my view, Appellants' argument further supports the Examiner's position: The skilled artisan would have

recognized that, even though a drug interacts with a tumor, it may not be effective in treating the tumor. To the extent Appellants are suggesting that a drug, without any interaction with the tumor, would be expected to provide effective treatment, I disagree, finding Appellants provided no evidence supporting such an argument.

Appellants' limited disclosure, i.e., their "contribution," is not commensurate in scope with the broad claims they seek. Thus, they should not be granted a patent that would exclude others from practicing the claimed invention for a substantial period of time.

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Paper No. 49

UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE BOARD OF PATENT APPEALS AND INTERFERENCES

Ex parte DAVID PORUBEK,
ANIL M. KUMAR, and
CHARLES R. BREDL

Appeal No. 2001-1101
Application No. 08/932,834

ON BRIEF

Before WINTERS, WILLIAM F. SMITH, and GREEN, Administrative Patent Judges.

WINTERS, Administrative Patent Judge.

DECISION ON APPEAL

This appeal was taken from the examiner's decision rejecting claims 1, 2, 4, 6, 7, 9, 10, 12 through 16, 18 through 21, and 23 through 27, which are all of the claims remaining in the application.

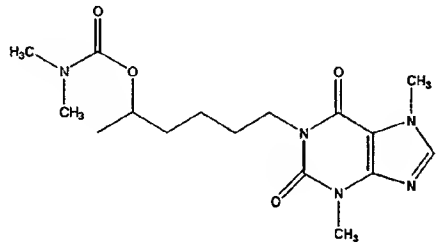
The Invention

The invention relates to compounds that form the hydroxy-substituted zanthine, lisofylline, in vivo. These compounds, or prodrugs, are said to possess a primary, characteristic benefit, viz., selective enantiomeric stability coupled with varying

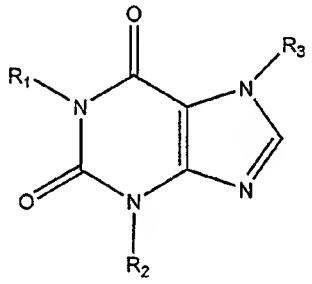
resistance to hydrolysis (Specification, paragraph bridging pages 5 and 6).

Claim 1, which is illustrative of the subject matter on appeal, reads as follows:

1. A compound having the following structure:

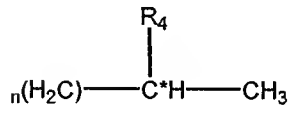


or a structure according to formula I:



I

wherein R_1 has the formula II:



R_2 and R_3 are independently $C_{(1-12)}$ alkyl, optionally, R_2 having one or two nonadjacent carbon atoms of the $C_{(1-12)}$ alkyl being replaced by an oxygen atom; and wherein:

C* is a chiral carbon atom;

n is four;

R_4 is a naturally occurring amino acid or a carbohydrate-moiety attached by an oxygen atom to the chiral carbon atom C* by an ester linkage, -O-X-$(R_5)_m$; m being two or three, depending on valence, and X being selected from the group consisting of C, P or S; wherein one R_5 is =O and any other R_5 is a member independently selected from Group Q,

said carbohydrate moiety is selected from the group consisting of glucosyl, glucosidyl, maltosyl, glucopyranosidyl, glyceraldehydyl, erythrosyl, arabinosyl, ribolucosyl, fructosyl, erythritolyl, xylosyl, lyxosyl, allosyl, altrosyl, mannosyl, mannosidyl, gulosyl, idosyl, galactosyl and talosyl, and

Group Q consists of:

hydroxyl group;

substituted or unsubstituted $C_{(3-10)}$ alkyl, $C_{(2-10)}$ alkenyl, $C_{(2-10)}$ alkynyl, $C_{(1-10)}$ alkoxyl, $C_{(1-10)}$ oxoalkyl, $C_{(1-10)}$ carboxyalkyl, $C_{(1-10)}$ hydroxyalkyl, or substituted $C_{(1-2)}$ alkyl group;

-OR_6, R_6 being a substituted or unsubstituted $C_{(1-10)}$ alkyl, $C_{(2-10)}$ alkenyl, $C_{(2-10)}$ alkynyl, or $C_{(1-10)}$ oxoalkyl;

substituted or unsubstituted heterocylic group, attached to X through an atom within the ring, having one or two rings, each ring containing from four to seven atoms, wherein the heteroatom(s) of said heterocyclic group is 1 or 2 nitrogens; and

substituted or unsubstituted carbocyclic group that is attached to X through a carbon atom within a ring, having one or two rings, each ring containing four to seven atoms, wherein the substituents of said substituted carbocyclic group are selected from the group consisting of amino, $C_{(2-6)}$ alkenyl, $C_{(1-6)}$ alkyl, $C_{(1-6)}$ alkoxyl, $C_{(1-6)}$ hydroxyalkyl, hydroxyl, $C_{(1-6)}$ oxoalkyl, azido, cyano, $C_{(2-6)}$ mono- or di-haloalkyl, isocyano, isothiocyano, imino, a chlorine atom, a bromine atom, a fluorine atom and an oxygen atom.

Prior Art

In rejecting the appealed claims under 35 U.S.C. § 112, first and second paragraphs, the examiner does not rely on any prior art references (Examiner's Answer, Paper No. 43, Section (9)).

The Rejections

Claims 1, 2, 4, 6, 7, 9, 10, 12, 13, 15, 16, 18 through 21, and 23 through 27 stand rejected under 35 U.S.C. § 112, second paragraph, as not particularly pointing out and distinctly claiming the subject matter which applicants regard as their invention.

Claims 1, 2, 4, 6, 7, 9, 10, 12 through 16, 18 through 21, and 23 through 27 stand rejected under 35 U.S.C. § 112, first paragraph, as based on a specification which does not adequately teach any person skilled in the art how to use the claimed invention.

Deliberations

Our deliberations in this matter have included evaluation and review of the following materials: (1) the instant specification, including Figures 1 through 10 and all of the claims on appeal; (2) the amended Appeal Brief (Paper No. 42); (3) the Examiner's Answer (Paper No. 43); and (4) the Paradise Declaration, filed under the provisions of 37 CFR § 1.132, executed June 17, 1999 (Paper No. 32).

On consideration of the record, including the above-listed materials, we affirm the examiner's rejection of claims 1, 2, 4, 6, 7, 9, 10, 12, 13, 15, 16, 18 through 21, and 23 through 27 under 35 U.S.C. § 112, second paragraph. We reverse the rejection of claim 14 under 35 U.S.C. § 112, first paragraph, and we do not reach the rejection of the remaining claims under that statutory provision.

Preliminary Matter

As a preliminary matter, we refer to section VII of the amended Appeal Brief

entitled "GROUPING OF THE CLAIMS." Applicants ask that we consider two groups of claims separately, stating that "[c]ompound claims 1, 2, 4, 6, 7, 9, 10, and 12-14 are patentable regardless of whether pharmaceutical composition claims 15, 18-21 and 23-27 are patentable" (Paper No. 42, Section VII). That section of the Appeal Brief, however, makes little sense. First, applicants have not set forth a grouping of claims "for each ground of rejection which appellant contests" as required by 37 CFR § 1.192(c)(7) (1999). Second, applicants have omitted claim 16 from their grouping of claims. Third, applicants' statement to the contrary, notwithstanding, claims 20, 21, and 23 through 27 are drawn to compounds, not pharmaceutical compositions.

Nonetheless, applicants' error in grouping claims for purposes of this appeal may be viewed as "harmless error" in view of our disposition of each ground of rejection discussed infra.

35 U.S.C. § 112, Second Paragraph

As stated in In re Zletz, 893 F.2d 319, 321-22, 13 USPQ2d 1320, 1322 (Fed. Cir. 1989): "An essential purpose of patent examination is to fashion claims that are precise, clear, correct, and unambiguous. Only in this way can uncertainties of claim scope be removed, as much as possible, during the administrative process." In the

Answer (Paper No. 43), the examiner points to several aspects of the appealed claims which are incorrect, indefinite, ambiguous, or simply make no sense. We shall not belabor the record on this point, because we agree substantially with the examiner's analysis. For reasons ably set forth by the examiner in the Answer, we affirm the rejection of claims 1, 2, 4, 6, 7, 9, 10, 12, 13, 15, 16, 18 through 21, and 23 through 27 under 35 U.S.C. § 112, second paragraph, as not particularly pointing out and distinctly claiming the subject matter which applicants regard as their invention.

We here note that the examiner rejected all claims in the application, except claim 14, under 35 U.S.C. § 112, second paragraph. Our affirmance of that rejection constitutes a disposition of the appeal with respect to all claims except claim 14.

35 U.S.C. § 112, First Paragraph

The remaining issue is whether the examiner erred in rejecting all of the appealed claims under 35 U.S.C. § 112, first paragraph, as based on a specification which does not adequately teach any person skilled in the art how to use the claimed invention. Under the circumstances, however, we shall not reach the merits of the "how to use" rejection with respect to claims 1, 2, 4, 6, 7, 9, 10, 12, 13, 15, 16, 18 through 21, and 23 through 27. Again, those claims are indefinite within the meaning of 35 U.S.C. § 112, second paragraph; they are not precise, clear, correct, and unambiguous. We think it imperative to understand the metes and bounds of the claims before proceeding to a resolution of an examiner's rejection under 35 U.S.C. § 112, first paragraph. Cf. In re Steele, 305 F.2d 859, 862, 134 USPQ 292, 295 (CCPA 1962)(Before deciding a rejection under 35 U.S.C. § 103, "it is essential to know what the claims do in fact

cover").

We now turn to a consideration of claim 14, cast in Markush format and reciting, in the alternative, 15 prodrugs of lisofylline. The examiner argues that it would require undue experimentation "to get lisofylline to actually work" (Paper No. 43, page 7, line 7). It follows, according to the examiner, that applicants' specification does not teach any person skilled in the art how to use the prodrugs recited in claim 14 without undue experimentation. In other words, the examiner's argument centers on lisofylline. If persons skilled in the art know how to use lisofylline, within the meaning of 35 U.S.C. § 112, first paragraph, the examiner would not deny that such persons would also know how to use the 15 prodrugs recited in claim 14.

It is uncontroverted on this record that "lisofylline is the subject [of] FDA-sanctioned Phase II and Phase III clinical trials." See the Paradise Declaration, filed under the provisions of 37 CFR § 1.132, executed June 17, 1999, paragraph 3 and Appendix E. As stated in In re Brana, 51 F.3d 1560, 1568, 34 USPQ2d 1436, 1442-43 (Fed. Cir. 1995), in the context of a PTO rejection under 35 U.S.C. § 112, first paragraph,

> Were we to require Phase II testing [FDA-sanctioned Phase II trials] in order to prove utility, the associated costs would prevent many companies from obtaining patent protection on promising new inventions, thereby eliminating an incentive to pursue, through research and development, potential cures in many crucial areas such as the treatment of cancer.

A fortiori, that lisofylline is the subject of FDA-sanctioned Phase II and Phase III clinical trials establishes, on this record, that any person skilled in the art knows how to use lisofylline within the meaning of 35 U.S.C. § 112, first paragraph. As stated in the Paradise Declaration, paragraph 3., "[m]erely getting such trials approved require [sic]

substantial indications of therapeutic efficacy." Accordingly, the premise of the examiner's rejection is incorrect and the rejection cannot be sustained.

Further, the examiner argues that applicants' specification does not provide useful daily dosage information (Paper No. 43, page 10, last full paragraph; and paragraph bridging pages 10 and 11). We would agree that there is room for improvement in applicants' description of a dosage regimen at page 9, first full paragraph of the specification. That passage, standing alone, is somewhat unclear. This does not, however, end the inquiry. Rather, the specification must be considered in its entirety taking into account the level of skill in the art. The following passage appears in the specification, page 9, second full paragraph:

> While dosage values will vary, therapeutic compounds of the invention may be administered to a human subject requiring such treatment as an effective oral dose of about 50 mg to about 5000 mg per day, depending upon the weight of the patient. For any particular subject, specific dosage regimens should be adjusted to the individual's need and to the professional judgment of the person administering or supervising the administration of the inventive compounds.

In our judgment, the above-quoted passage adequately conveys to any person skilled in the art useful daily dosage information for the claimed compounds.

The examiner's rejection of claim 14 under 35 U.S.C. § 112, first paragraph, is reversed.

Conclusion

In conclusion, for reasons set forth in the body of this opinion, we sustain the examiner's rejection of claims 1, 2, 4, 6, 7, 9, 10, 12, 13, 15, 16, 18 through 21, and 23 through 27 under 35 U.S.C. § 112, second paragraph.

We do not reach the merits of the "how to use" rejection under 35 U.S.C. § 112, first paragraph, with respect to claims 1, 2, 4, 6, 7, 9, 10, 12, 13, 15, 16, 18 through 21, and 23 through 27.

We do not sustain the examiner's rejection of claim 14 under 35 U.S.C. § 112, first paragraph.

The examiner's decision is affirmed-in-part.

No time period for taking any subsequent action in connection with this appeal may be extended under 37 CFR § 1.136(a).

AFFIRMED-IN-PART

Sherman D. Winters
Administrative Patent Judge

William F. Smith
Administrative Patent Judge

Lora M. Green
Administrative Patent Judge

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